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Invited Review Article

Sweat is a most efficient natural moisturizer providing protective immunity at points of allergen entry

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AD, atopic dermatitis; FLG, filaggrin; HZ, herpes zoster; IMT, impression mold technique; DCD, demcidin; SC, stratum corneum; SSH, skin surface hydration; TEWL, transepidermal water loss; TJ, tight junction; VZV, varicella-zoster virus

ABSTRACT

Although there is a growing acceptance that sweat could play a detrimental role in various allergic skin diseases, the possibility that sweat is also involved in maintenance of skin hydration and skin-specific immune responses has not been acknowledged. We initially describe physiological role of sweat in both maintaining skin hydration and thermoregulation. The purpose of this article is to provide the reader with objective evidence that sweating is intimately linked to vital stratum corneum barrier function and usefulness of application of moisturizers in clinical care of allergic skin diseases. This review also covers how sweating disturbance would leave the skin vulnerable to the development of various allergic skin diseases, such as atopic dermatitis. New therapeutic approaches would specifically target such sweating disturbance in these allergic skin diseases.

Introduction

Sweat is well known to be one of important factors provoking exacerbations of clinical symptoms in many allergic skin diseases including atopic dermatitis (AD).[1] Because many patients with AD often complain of aggravation of pruritus and eczematous skin lesions after severe sweating, the prevailing dogma, shaped by such observations, depicts the detrimental role of sweat in the pathogenesis of allergic skin disease, while ignoring the protective role of sweat. However, recent studies have[2–5] revised this dogma and found that sweating can confer protective immunity under certain conditions. Indeed, the role of sweat in allergic inflammation is more complex than previous studies implied. In recent years, there is increasing evidence suggesting the protective role of sweat on allergic inflammation.

Dry skin is generally thought to be caused by defects in skin genes that are important for maintaining skin barrier function.[6,7] Compelling basic science investigations places genetic defects in barrier function as a key factor in barrier dysfunction. In contrast, the role of sweating in maintaining water in the stratum corneum (SC) has received no or little attention despite the overwhelming great capacity of sweat to increase skin surface hydration (SSH) (Fig. 1).[2,5] The importance of preserving sweating function, especially in those affected by AD, remains an under-recognized topic even by dermatologists. Although dry skin can be aggravated by environmental factors, such as ambient humidity and modern life style, and by the decreased ability to sweat, as well as genetic defects in skin barrier function, no recommendation is available about the effect of sweat on the maintenance of water in the SC, the role of sweat in barrier function, and the effect of moisturizers and other topical agents on sweating function. The purpose of this article is to provide the reader with objective evidence that sweating is

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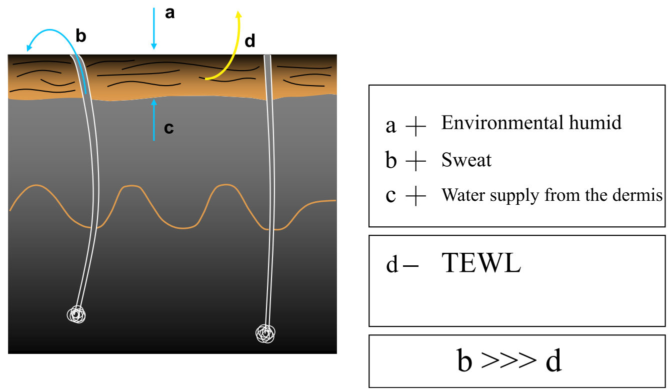

Fig. 1. Balance between water retention and water release in the SC. Humid environment, sweat and water supply from the dermis serve to hold and increase water content in the SC, while TEWL serves to lose water from the dermis. Decreased water content in the SC in dry skin would be theoretically compensated fully by increased sweating, given that sweat has much higher water content than TEWL.

intimately linked to vital SC barrier function and usefulness of application of moisturizers in clinical care. It is important to recognize that moisturizers are not all the same and that prescribing should be guided by the ability to preserve or restore SSH and sweating function.

Physiological roles of sweat glands/ducts

Most mammals have sweat glands but only limited mammals such as humans, horses and some breeds of cattle use sweating for thermoregulation in response to heat or exercise.[8] In humans, eccrine sweat glands are distributed widely on both hairy and glabrous skin, such as the palms and soles, with some exceptions.[9] In contrast, other mammals such as monkeys, dogs and mice, have eccrine glands only on glabrous skin, such as the paw. In other mammals, sweating is thought to be caused by emotional stress, either positive or negative stimuli: stress-induced sweating, unlike thermal-induced sweating, results from activation of both eccrine and apocrine glands in the axilla.[9] Sweat pores open at the dermal ridge on the palms and soles, while those on the hairy skin, such as forearms, usually open at the folds[10] (Fig. 2). According to our recent results, in hairy skin sweat pores usually open at the folds under baseline conditions but upon thermal stimuli also open at the ridge.[11] Based on these results, medical literature suggests that localization of sweat pores relative to skin creases and ridges is different depending on the anatomical sites.[10,11] These suggestions have been frequently misinterpreted as a total absence of eccrine glands/ducts in the folds on the palms and soles. There are substantial differences in function between sweat pores in hairy skin and glabrous skin: those located in the glabrous skin of the palms and soles secrete sweat in response to emotional or psychological stress, physical exercise, and high environmental temperatures. In contrast, those located in the hairy skin do not necessarily respond well to such stimuli. During evolution, the emergence of eccrine glands in glabrous skin has been suggested to precede that in the hairy skin. This classification, however, is too simplified because even in the hairy skin, sweat pores open not only at the skin folds but also at the ridges, and *vice versa* in glabrous skin.

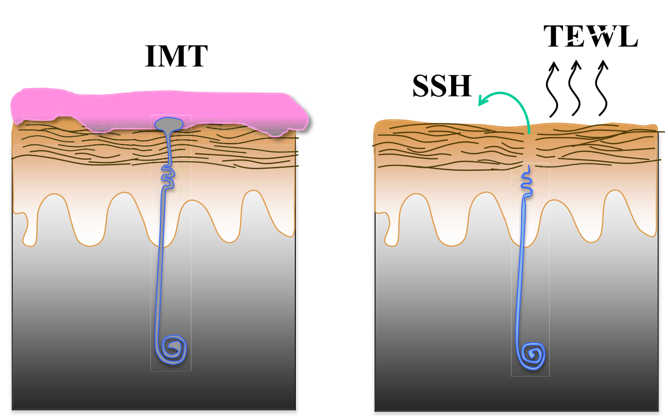

Fig. 2. Methods to quantitatively assess sweating responses. Output of sweat per a sweat gland/duct can be quantitatively assessed by IMT (Left), but not by previously used methods (right), in which exact output of sweat from a sweat gland/duct cannot be assessed. In previously used methods, sweating responses are estimated by the differences in TEWL and SSH levels before and after thermal stimulus.

To investigate whether the function of sweat would be different depending on the localization of sweat pores in relation to skin surface structures, we established a novel impression mold technique (IMT), which allows an accurate quantification of individual sweat gland/duct activity to secret sweat in a well-defined location and the volume of sweat they produce, repeatedly over time[2,5,11] (Fig. 3). With the use of IMT, we demonstrated that, under quiescent conditions, basal levels of sweat could be exclusively excreted from the sweat pores localized at the folds (basal or insensible sweating),[2,11] while increased levels of sweat would be also secreted from the pores at the ridge upon thermal stimulus (inducible or sensible sweating).[5,11] We also suggested that physiological roles of sweat glands/ducts would be different depending on the skin surface topography: the major function of sweat glands/ducts located at the folds is to maintain SSH while that of sweat glands/ducts at the ridges might serve as a backup to impaired function of sweat glands/ducts at the folds or as a thermoregulatory[5,11] (Fig. 2). In view of the possible function of sweat glands/ducts on the hairy skin, we can hypothesize that sweat glands/ducts at the ridges may secrete sweat when exposed to different humidity levels, such as exposure to water. Indeed, our unpublished findings indicate that in the fingertip sweat pore openings became detected at the folds, where no sweat pore opening were detected at baseline, but not at the ridges 10 min after water immersion (Aoyama Y *et al.*, unpublished data). Ten min after drying, however, sweat pore opening detected at the folds disappeared coincident with the reappearance of sweat pore openings at the ridges, as before water immersion. In contrast, such alterations of sweating responses after exposure to water depending on sweat glands/duct at the ridges/folds were never observed in hairy skin. These results could be interpreted as suggesting that sweat glands/ducts at the folds in glabrous skin would secrete sweat upon exposure to water, thereby maintaining water at the folds.

The relationship between SSH levels and basal sweating

According to our results of sweating responses evaluated by IMT(5, 11), sweat droplets corresponding to sweat pore openings were distributed evenly and usually occupied each dermal fold in hairy skin and were rarely detected in the ridges under quiescent conditions without thermal stimulus. In the IMT measurement, regional differences were minimal when examined in the forearm and abdomen. These results suggest that even under quiescent basal conditions basal levels of sweat could be excreted at the skin surface which may be reflected in the SSH levels (Fig. 3). We therefore asked whether there could be a true association between the SSH status and sweat volume as evidenced by numbers and sizes of sweat droplets detected at either the folds or ridges under quiescent basal conditions. A strong, positive correlation was found between the SSH status and sweat droplet numbers