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Cholinergic induction of perspiration attenuates non-histaminergic pruritus in the skin of atopic dermatitis subjects and healthy controls:

Sweat and itch in atopic dermatitis and healthy controls

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Dear Editor,

Although dry skin and barrier impairment are key drivers for itch induction in atopic dermatitis (AD), many other factors can impact itch intensity. In particular, AD patients often report that autologous sweating aggravates their itch¹. Indeed, AD lesions are characteristically distributed in regions where sweat glands are prominent, such as the neck, face, wrists, and cubital and popliteal fossae. Additionally, sweat is known to influence the pH of skin, which plays a crucial role in the pathogenesis of skin dermatoses such as AD².

The association between perspiration and pruritus is of great clinical importance, yet no experimental model has been developed to assess this relationship. To address this issue, we conducted a controlled-cohort study to evaluate the effects of localized, cholinergically induced perspiration on the intensity of non-histaminergic induced itch (see Supplement). In the baseline sweat condition, sweat was induced by pilocarpine iontophoresis on healthy (n=10) and AD (n=10) subjects' forearms. Sweat was collected for 30 minutes, and activated sweat glands (ASG) were counted after sweat collection. In the baseline itch condition, itch was induced using cowhage, which activates PAR2 receptors³, which have been shown to play a role in the itch of AD⁴. Subjects rated itch intensity using a visual analogue scale (VAS) for the duration of the itch sensation. In the combined sweat and itch condition, itch was induced immediately following sweat induction. Sweat was collected and itch intensity was rated as before. We hypothesized that sweating would increase itch intensity in both AD and healthy subjects.

The average VAS itch for the AD subjects for two weeks before the experiment was 5.5 ± 2.3 , while the average Eczema Area and Severity Index score was 21.2 ± 20.1 . AD subjects reported that the forearm and thigh areas itched most often and that their pruritus-related

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QOL was most affected by “temperature or seasonal changes,” with an average frequency score of 4.13 ± 0.38 . Of note, 60% of subjects reported that sweat exacerbated their itch.

In the baseline sweat condition, healthy and AD subjects produced statistically similar amounts of sweat (0.48 ± 0.2 g vs. 0.42 ± 0.15 g). AD subjects produced less sweat when itch and sweat were induced together (0.22 ± 0.03 g) compared to baseline sweat alone ($p=0.02$). Healthy subjects did not significantly differ in sweat production during the sweat and itch condition (0.36 ± 0.18 g) compared to baseline sweat. Furthermore, AD subjects produced significantly less sweat than healthy controls during the combined itch and sweat condition ($p=0.04$; Fig. 1A). Although some prior reports have shown a reduced sweat response in AD subjects upon cholinergic stimulation^{5–7}, another study found no difference in the volume of sweat produced by AD and healthy subjects with either pilocarpine-induced sweat or emotional sweat⁸. The amount of sweat collected from AD subjects was significantly decreased during the combined itch and sweat condition compared to baseline sweat. However, ASG counts were statistically similar in all conditions (Fig. 1B–D), suggesting that they were not responsible for the change in sweat production.

During the baseline itch condition, the overall time course of itch intensity did not differ significantly between healthy and AD subjects. This result matches our previous observations for non-eczematous skin⁹. Contrary to our hypothesis, AD subjects showed no significant change in itch intensity during the combined sweat and itch condition compared to the itch baseline, while healthy subjects displayed a significant decrease in itch intensity ($p=0.01$; Fig. 1E). Additionally, when comparing the area under the curve (AUC), which represents the total itch perceived, both healthy ($p=0.03$) and AD ($p=0.01$) subjects had significantly less itch during the combined sweat and itch condition compared to the itch baseline (Fig. 1F). The AUC was lower in healthy subjects than in AD subjects during the combined sweat and itch condition ($p=0.02$), but not during the baseline itch condition. Interestingly, no statistical differences were found when comparing the results of AD subjects who reported sweat as an aggravating factor in their itch compared to those who did not.

We also hypothesized that sweat pH may have a role in aggravating itch, so in a second study visit, we explored the effects of sweat pH on itch intensity using artificial sweat solutions with differing pH values (4.2, 5.2, and 7.2). These artificial solutions sweat were applied to the forearms after cowhage itch induction, and subjects rated their itch intensity as before. In both healthy and AD subjects, itch intensity did not differ during the application of any imitation sweat solution compared to the control application of water (Fig. 2A–B). A previous study found that skin surface pH was approximately 5.24 in healthy subjects, while AD patients displayed relatively elevated pH levels on non-lesional skin (pH 5.54)¹⁰. This change in pH has been associated with an increased perception of itch, possibly due to increased activity of pH-dependent serine proteases, which can alter the integrity and barrier function of the stratum corneum¹¹. Our artificial sweat solutions may have been restricted in their capacity to change the overall skin pH and to alter itch perception in subjects. We did not measure subjects' skin surface pH before or after application of the different artificial sweat preparations.

In conclusion, the results of our sweat model did not mimic the clinical observations of sweat as a major exacerbating factor of itch in AD patients. A major limitation of this study is that our model of sweat induction is pharmacological and thus may not mimic authentic, natural sweat, which has additional components (such as heat, emotional stress, sympathetic reflex, and adrenergic signaling) that can aggravate chronic itch^{12–14}. In addition, future studies should examine both eczematous and unaffected skin, as there have been noted differences in sweat volume, sweat latency, and skin surface pH in lesional versus non-lesional sites^{5,10}. In an abnormal cutaneous barrier, sweat can penetrate more deeply, activate epidermal keratinocytes, and stimulate pro-inflammatory cytokine production¹⁵. Studies on the molecular makeup of sweat could also elucidate the relationship between sweat and itch.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) The amount of sweat produced did not differ between healthy and AD subjects. However, AD subjects produced less sweat while itching compared to their sweat baseline and compared to healthy subjects during sweat and itch (* $p < 0.05$). (b) Healthy and AD subjects did not differ in the number of sweat glands that were activated, and itching did not cause a change in sweat gland activation in either group. Representative images of iodine-paper showing activated sweat glands in healthy skin (c) and AD (d). (e) Sweat induction concurrent with itch induction (closed symbols) resulted in reduced VAS itch ratings for both healthy (black) and AD subjects (red). However, only healthy subjects showed a significant ($p < 0.05$) change from baseline itch (open symbols). (f) Area under the curve (AUC), representing the total itch perceived, was significantly reduced from baseline when itch was induced with sweat in both groups (* $p < 0.05$, ** $p < 0.01$). Furthermore, the AUC for healthy subjects was significantly different from AD subjects during the itch and sweat condition (* $p < 0.05$).

Figure 2.

The differing pH values (4.2, 5.2, and 7.2) of imitation sweat did not significantly affect the itch VAS intensities in healthy (a) or AD subjects (b) compared to a water (pH 7) control.