

# Repetitive scratching and noxious heat do not inhibit histamine-induced itch in atopic dermatitis

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## Summary

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### Key words

atopic dermatitis, itch, psychophysics, quantitative sensory testing, sensitization

### Conflicts of interest

None declared.

**Background** Repetitive scratching is the most common behavioural response to itch in atopic dermatitis (AD). Patients with chronic itch often report that very hot showers inhibit itch. We recently reported that scratching and noxious heat stimuli inhibit histamine-induced itch in healthy subjects. However, no psychophysical studies have been performed in AD to assess the effects of repetitive heat pain stimuli and scratching on histamine-induced itch.

**Objectives** To examine the effects of repetitive noxious heat and scratching on itch intensity in patients with AD using quantitative sensory testing devices.

**Methods** Itch was induced with histamine iontophoresis in 16 patients with AD in both lesional and nonlesional skin as well as in 10 healthy subjects. Repetitive noxious heat and scratching were applied 3 cm distal to the area of histamine iontophoresis. Subjects rated their perceived intensity of histamine-induced itch with a computerized visual analogue scale.

**Results** Our results demonstrate that repetitive noxious heat and scratching do not inhibit itch intensity in lesional and nonlesional AD skin but do so in healthy skin. Of note, both these stimuli increase itch intensity in lesional AD skin.

**Conclusions** Our results strongly suggest that scratching and noxious thermal stimuli have a different effect upon histamine-induced itch perception in patients with AD when compared with healthy controls. This difference may be associated with both peripheral and central sensitization of nerve fibres in AD.

Patients with atopic dermatitis (AD) often describe 'an itch that they cannot stop scratching'. For decades, the application of painful stimuli has been suggested as a method to inhibit itch. Consistent with this notion, studies using questionnaires have revealed that patients with AD frequently report relief of their itch following painfully hot showers.<sup>1,2</sup>

Itch inhibition by painful stimuli has been demonstrated in experimental models using various painful thermal, mechanical and chemical stimuli.<sup>3</sup> We recently reported that histamine-induced itch was reduced in healthy volunteers by repetitive noxious heat pain and scratching distal to the area of itch induction.<sup>4</sup>

Recent data demonstrate that single application of painful stimuli (electrical, chemical, mechanical or thermal) is perceived as itch when applied on or close to lesional skin in patients with AD.<sup>5,6</sup> It has already been suggested that neural sensitization is involved in this altered itch perception in AD.<sup>7</sup> The purpose of the current study was to examine the effect of repetitive noxious heat and scratching on itch intensity in lesional and nonlesional skin of patients with AD using quantitative sensory testing methods.

## Patients and methods

### Subjects

A total of 26 subjects all between 19 and 59 years of age participated in this study (mean  $\pm$  SD 34.3  $\pm$  11.4): 16 with AD (seven men and nine women) and 10 healthy volunteers (five men and five women). Healthy volunteers were matched for age and gender. AD was diagnosed by the criteria of Hanifin and Rajka.<sup>8</sup> The Eczema Area and Severity Index (EASI) score of the patients with AD showed three patients with mild, eight with moderate and five with severe disease.<sup>9</sup> All procedures were approved by the Institutional Review Board of Wake Forest University School of Medicine. All subjects provided written informed consent.

### Induction of itch sensation

Itch was evoked by iontophoresis of histamine into both lesional and nonlesional skin of the ventral forearm skin in patients with AD as well as into skin at the ventral forearm of

healthy controls using a round iontophoresis electrode 14 mm in diameter. Histamine was chosen as the itch stimulus as it is the most familiar pruritogen and is still frequently used in both human and animal experimental itch models. For iontophoresis, a 1% solution of histamine was dissolved in 2% methylcellulose gel (Sigma, St Louis, MO, U.S.A.) and was administered with a current of 200  $\mu$ A for 30 s (Perilont PF3826 Power device; Perimed, Stockholm, Sweden). A vehicle control stimulus of 0.9% saline in 2% methylcellulose gel was administered (200  $\mu$ A for 30 s) in order to control for expectations of itch. Iontophoresis was terminated 30 s prior to any thermal and scratch stimuli. Histamine iontophoresis was performed three times during the experimental session. Each itch trial was performed following an interval of 10 min.

### Stimuli modulating itch

All modulatory stimuli were applied to sites on the ventral forearm 3 cm distal to the edge of the area of histamine iontophoresis. We chose to induce noxious stimuli 3 cm away from the site of itch induction because in our previous study using healthy subjects we had shown that histamine-induced itch was inhibited by noxious thermal stimuli and scratching at this site.<sup>4</sup> The noxious heat stimuli and scratching were always induced at nonlesional regions regardless of the itch stimulation site of lesional or nonlesional skin. Thermal stimuli were delivered by a 16  $\times$  16 mm Peltier device (TSA 2001; Medoc, Ramat Yishai, Israel). Thermal stimulus was noxious heat (49 °C). Thermal stimulation started 30 s after termination of histamine iontophoresis and was cycled between 30-s duration applications of the thermal stimulus and 30-s duration applications of the neutral control stimulus (32 °C). Scratching was accomplished by study personnel repetitively moving a cytology brush (Medi-Pak 7-inch cytology brush 24–2199; General Medical Corporation, Richmond, VA, U.S.A.) over the ventral forearm 3 cm distal to the iontophoresis site. A full description of this method has been previously reported.<sup>4,10</sup> Itch stimuli, heat pain and scratching were induced in the following order: saline iontophoresis, scratching, heat pain, histamine, histamine with scratching and histamine with heat pain. Nonlesional areas were examined firstly for the patients with AD.

### Quantitative psychophysical measurements

Subjects used a 100-mm computerized visual analogue scale (COVAS; Medoc) for continuous reporting of perceived intensity of histamine-induced itch in the presence and absence of modulatory stimuli ranging from 0 (no sensation) to 100 mm (most intense sensation imaginable). Of note, the COVAS scale functions as a true ratio scale.<sup>11</sup> Firstly, itch intensity was rated during scratching and pain sensation was rated during heat pain in the absence of itch in both lesional and nonlesional skin. Then itch sensation was measured during histamine, histamine with scratching and histamine with heat pain stimulus in both lesional and nonlesional skin.

### Flare

The visually estimated longest and shortest axes of the evoked flare areas were measured with a ruler, 300 s after histamine iontophoresis in both lesional and nonlesional skin. The mean of the long and short axes was regarded as the area diameter and was used for statistical analysis.

### Statistical analysis

To simplify analyses of continuous COVAS data, itch intensity ratings were extracted from the midpoints of each period of modulatory stimulation and analogous time points of control stimulation. Psychophysical ratings of itch were then analysed using two-factor (time  $\times$  modulatory stimulus) repeated-measures analyses of variance (JMP software; SAS Institute, Cary, NC, U.S.A.) to determine changes in sensations due to modulatory stimuli and due to time. There were two levels of the modulatory stimulus factor (baseline vs. modulatory stimulus) and, depending on the modulatory stimulus, there were six or seven levels of the time factor. A significant main effect of either the modulatory stimulus factor or a significant interaction between the modulatory stimulus and time factors indicates that the perception of itch is significantly influenced by the presence of the modulatory stimulus.

To evaluate the relationship between interindividual differences in thermal sensitivity and histamine-induced itch sensitivity, Spearman's correlation tests were performed between the peak intensity ratings of each modulatory stimulus and the peak intensity ratings of itch. Statistical analyses of diameters of flare reaction, itch intensity and disease severity were performed using two-sample paired *t*-test, analysis of variance, and the Pearson's correlation test. Data are presented as mean  $\pm$  SD; *P* < 0.05 is considered statistically significant.

## Results

### Baseline itch intensity with histamine and saline iontophoresis

Following histamine iontophoresis, mean and peak itch intensities in lesional skin were significantly higher than in both nonlesional and healthy skin (Table 1). There was no significant difference in the mean and peak itch intensities between nonlesional and healthy skin (Table 1). Mean and peak itch intensities did not differ among all three skin groups (lesional, nonlesional and healthy skin) following saline iontophoresis (Fig. 1 and Table 1).

In lesional skin, itch intensity increased immediately following histamine stimulation, increasing gradually for 120 s to reach a peak intensity, and thereafter plateaued for the rest of the examination (Figs 2, 3). In nonlesional skin and in healthy skin, after a latent period of about 30 s following histamine stimulation, itch intensity gradually increased for about 40 s

Table 1 Mean  $\pm$  SD and peak itch intensity by visual analogue scale

| Testing stimulus                       | Healthy skin |             | Nonlesional skin |             | Lesional skin |             |
|----------------------------------------|--------------|-------------|------------------|-------------|---------------|-------------|
|                                        | Mean         | Peak        | Mean             | Peak        | Mean          | Peak        |
| Saline <sup>abc</sup>                  | 2 $\pm$ 2    | 9 $\pm$ 10  | 7 $\pm$ 9        | 20 $\pm$ 19 | 11 $\pm$ 16   | 28 $\pm$ 32 |
| Histamine <sup>def</sup>               | 7 $\pm$ 7    | 22 $\pm$ 12 | 16 $\pm$ 16      | 32 $\pm$ 25 | 43 $\pm$ 30   | 69 $\pm$ 34 |
| Histamine with scratch <sup>ghi</sup>  | 3 $\pm$ 2    | 10 $\pm$ 8  | 22 $\pm$ 23      | 45 $\pm$ 33 | 46 $\pm$ 23   | 74 $\pm$ 31 |
| Histamine with heat pain <sup>kl</sup> | 5 $\pm$ 8    | 15 $\pm$ 12 | 23 $\pm$ 17      | 49 $\pm$ 35 | 39 $\pm$ 27   | 73 $\pm$ 34 |

<sup>a</sup>Healthy skin vs. nonlesional skin: mean  $P = 0.3$ , peak  $P = 0.3$ . <sup>b</sup>Healthy skin vs. lesional skin: mean  $P = 0.3$ , peak  $P = 0.1$ . <sup>c</sup>Nonlesional skin vs. lesional skin: mean  $P = 0.6$ , peak  $P = 0.6$ . <sup>d</sup>Healthy skin vs. nonlesional skin: mean  $P = 0.3$ , peak  $P = 0.4$ . <sup>e</sup>Healthy skin vs. lesional skin: mean  $P = 0.001$ , peak  $P = 0.003$ . <sup>f</sup>Nonlesional skin vs. lesional skin: mean  $P = 0.008$ , peak  $P = 0.008$ . <sup>g</sup>Healthy skin vs. nonlesional skin: mean  $P = 0.005$ , peak  $P = 0.005$ . <sup>h</sup>Healthy skin vs. lesional skin: mean  $P = 0.0001$ , peak  $P = 0.0001$ . <sup>i</sup>Nonlesional skin vs. lesional skin: mean  $P = 0.008$ , peak  $P = 0.008$ . <sup>j</sup>Healthy skin vs. nonlesional skin: mean  $P = 0.07$ , peak  $P = 0.05$ . <sup>k</sup>Healthy skin vs. lesional skin: mean  $P = 0.0001$ , peak  $P = 0.0001$ . <sup>l</sup>Nonlesional skin vs. lesional skin: mean  $P = 0.01$ , peak  $P = 0.01$ .

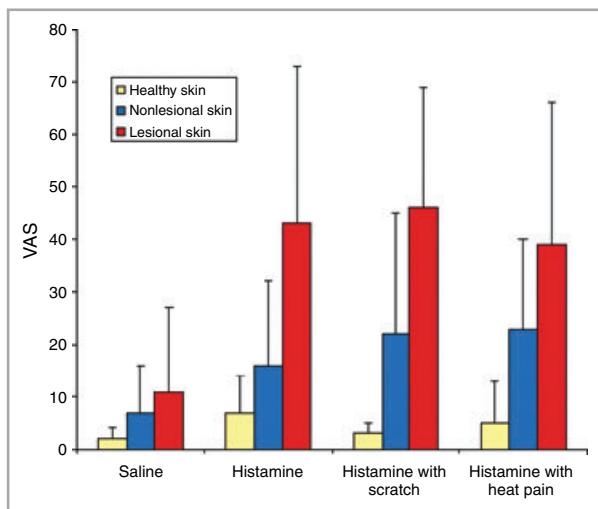


Fig 1. Mean  $\pm$  SD itch intensity as measured by visual analogue scale (VAS) of histamine-induced itch in lesional (red) and nonlesional atopic dermatitis (blue) skin as well as healthy skin (yellow). A significant difference in itch intensity is noted between healthy skin and both lesional and nonlesional skin. Repetitive noxious heat and scratching do not inhibit itch intensity in lesional and nonlesional atopic dermatitis skin but do so in healthy skin.

to reach peak intensity and then plateaued (nonlesional skin) or gradually decreased (healthy skin) for the remainder of the examination (Figs 2, 3).

### Repeated noxious heat does not inhibit itch intensity in atopic dermatitis

The pattern of histamine-induced itch intensity with heat pain was similar in both lesional and nonlesional AD skin. Itch intensity ratings exhibited an increasing trend during each period of heat pain stimulus for both lesional and nonlesional skin but did not reach statistical significance (Fig. 2a,b). During the off period of noxious heat stimuli, the itch intensity

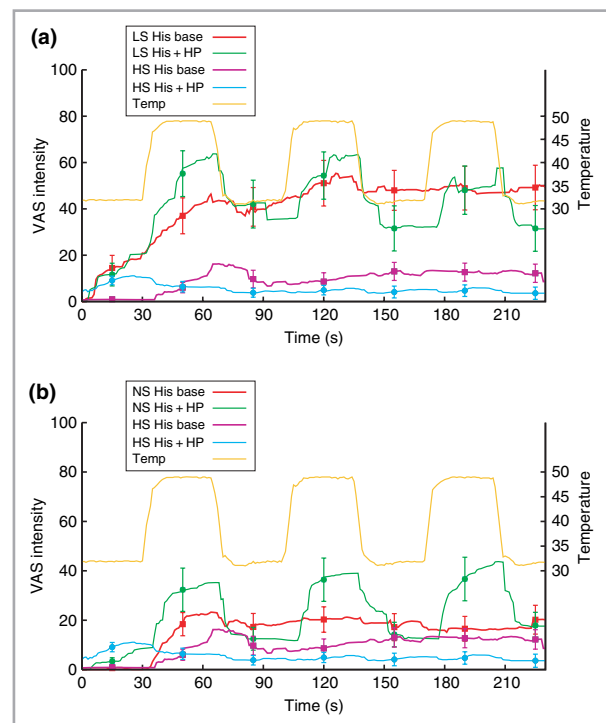


Fig 2. (a) Mean  $\pm$  SD itch intensity in lesional atopic dermatitis skin with histamine alone (red) and with histamine and noxious heat (49 °C) (green), 3 cm distal to site of histamine iontophoresis. At the onset of noxious heat stimulation, itch ratings increased in lesional skin. At the offset of the 30-s stimuli a quick reduction in itch intensity is noted. The mean and peak responses of itch in lesional skin are significantly higher than in nonlesional skin. However, heat pain reduced itch in healthy skin (blue). (b) Mean  $\pm$  SD itch intensity in nonlesional skin. At the onset of noxious heat stimulation, itch ratings increased and at the offset of the stimuli a significant quick reduction in itch intensity in nonlesional skin is noted in a similar pattern to lesional skin. However, heat pain reduced itch in healthy skin (blue). LS, lesional skin; HS, healthy skin; NS, nonlesional skin; His, histamine; HP, heat pain; Base, baseline; Temp, temperature (°C).

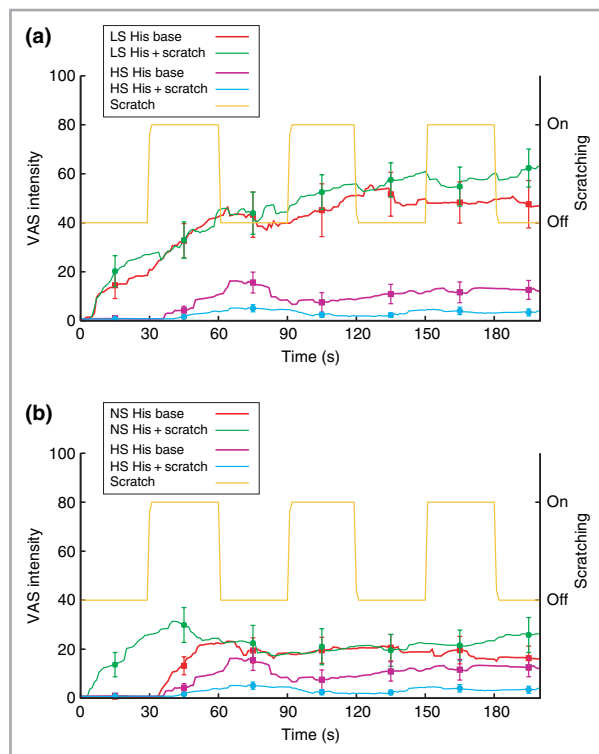


Fig 3. (a) Mean  $\pm$  SD itch intensity in lesional skin with histamine alone (red) and with histamine and repetitive scratching with a cytology brush (green), 3 cm distal to site of histamine iontophoresis. Scratching slightly increased itch in lesional skin. This was sustained for the duration of the scratching stimuli. However, scratching reduced itch in healthy skin (blue). (b) Mean  $\pm$  SD itch intensity in nonlesional skin. Repetitive scratching did not change itch intensity in comparison with histamine alone in nonlesional skin. However, scratching reduced itch in healthy skin (blue). LS, lesional skin; HS, healthy skin; NS, nonlesional skin; His, histamine; Base, baseline.

decreased to a level slightly lower than that of baseline. Mean and peak itch intensities with heat pain were significantly higher in lesional compared with nonlesional AD skin (Fig. 1 and Table 1).

In healthy skin, histamine-induced itch intensity ratings were significantly reduced during each period of noxious heat ( $P < 0.0001$ , Fig. 2). Itch ratings decreased immediately upon the onset of heat pain and remained at a low level during the entire period of stimulation. There was a significant difference in histamine-induced itch with heat pain between healthy skin and both lesional and nonlesional AD skin (Fig. 1 and Table 1). Of note, all patients reported pain on application of noxious heat stimuli alone (i.e. without histamine iontophoresis).

#### Repeated scratching does not inhibit itch intensity in atopic dermatitis

All examinees perceived scratching with the cytology brush as similar to their own experience of scratching. In lesional skin, scratching did not inhibit histamine-induced itch intensity but, in fact, slightly increased it (Fig. 3a); however, this effect

did not reach statistical significance. In nonlesional skin, itch intensity during histamine with scratching was similar to that induced by histamine alone (Fig. 3b). Mean and peak itch intensities induced by histamine with scratching in lesional skin were significantly higher than in nonlesional and healthy skin (Fig. 1 and Table 1).

In healthy skin, histamine-induced itch intensity ratings were significantly reduced during each period of scratching ( $P < 0.02$ , Fig. 3). Itch ratings decreased immediately at the onset of scratching and remained at low levels during the entire period of scratching. Mean and peak itch intensities induced by histamine with scratching in healthy skin were significantly lower than in lesional and nonlesional AD skin (Fig. 1 and Table 1). Of note, baseline scratch (i.e. without histamine iontophoresis) did not induce itch in healthy control skin. However, it did induce itch near lesional and nonlesional skin of subjects with AD ( $19.9 \pm 26.2$  and  $8.5 \pm 14.1$ , respectively). There was no significant difference in scratch-induced itch between lesional and nonlesional skin of AD ( $P = 0.150$ ).

#### Interindividual differences in itch and heat pain sensitivity

No significant difference in pain sensitivity was noted between lesional, nonlesional skin and healthy skin. Interindividual differences in the magnitude of histamine-induced itch intensity were weakly correlated with interindividual differences in the magnitude of heat pain intensity ratings in nonlesional skin ( $r^2 = 0.33$ ,  $P = 0.06$ ); however, they were not correlated in lesional skin ( $r^2 = 0.15$ ,  $P = 0.27$ ).

Significant interindividual differences in itch sensitivity to histamine were noted among the healthy subjects; however, interindividual differences in itch sensitivity were unrelated to interindividual differences in pain sensitivity. Interindividual differences in the magnitude of COVAS ratings of histamine-induced itch intensity were not significantly correlated with interindividual differences in the magnitude of heat pain intensity ratings ( $r^2 = 0.04$ ,  $P = 0.3$ ).

#### Flare

The mean diameter (cm) of the axon reflex erythema induced by histamine iontophoresis was significantly higher in healthy skin than in nonlesional skin ( $1.6 \pm 0.7$  vs.  $1.0 \pm 0.3$ ,  $P < 0.04$ ). However, there was no significant difference in histamine-induced flare reaction between lesional and both nonlesional and healthy skin. Heat pain and scratching produced no significant effect on histamine-induced flare reaction in lesional, nonlesional and healthy skin.

#### Correlation between itch intensity, disease severity and skin flare reaction

No correlation was observed between itch intensity, disease severity (as assessed by EASI score) and skin flare reaction for

lesional and nonlesional skin. In healthy subjects, no correlation was observed between itch intensity and skin flare reaction.

### Difference between men and women in itch intensity

No difference was noted between men and women in itch intensity following histamine, histamine with heat pain or histamine with scratching for all three skin groups.

## Discussion

It is a well-known physiological phenomenon that pain inhibits itch intensity when applied to the same or a proximal area of skin. Pain can reduce histamine-induced itch locally for several hours.<sup>3,10,12</sup> This has been explained by central inhibitory projections from nociceptive neurones on itch-mediating fibres.<sup>7</sup>

The current study provides further support that the itch modulation in AD is abnormal and could be associated with sensitization. This abnormal modulation is similar to the pain sensitization observed in patients with chronic pain. Histamine stimulation, which normally provokes itch, is perceived as painful in patients with chronic pain disorders such as complex regional pain syndrome<sup>13</sup> and postherpetic neuralgia,<sup>14</sup> indicating central sensitization of pain to pruritic stimuli. Ikoma *et al.*<sup>15</sup> have shown that patients with AD perceive thermal pain (when applied to lesional skin) and mechanical stimuli (when applied to lesional skin and 1 cm away) as itch, and explained this as central sensitization.<sup>7</sup> Of note, histamine itself has been suggested to evoke hyperknesis (perception of itch being more intense than normal) in healthy subjects; however, this was not our observation.<sup>16</sup> Scratch and noxious heat stimuli were induced 3 cm distal to the site of histamine application in the current study. Interestingly, we show that scratch stimulus alone induces an itch sensation in both lesional and nonlesional skin but not in healthy control skin. Given that pain was the overriding sensation when only noxious heat stimulus was applied to our study population, we did not gather data regarding itch sensation. Future studies addressing whether a noxious stimulus alone can induce itch in lesional and nonlesional skin of subjects with AD would be of high interest.

We demonstrate that repetitive noxious heat and scratching do not inhibit histamine-induced itch intensity in lesional and nonlesional AD skin but do so in healthy skin (noxious stimuli were applied 3 cm distal to the site of histamine iontophoresis). Moreover, the axon reflex (an indirect measure of peripheral afferent nerve fibre activity) did not differ between lesional, nonlesional and healthy skin following histamine application. The fact that both lesional and nonlesional AD skin display abnormal modulation of histamine-induced itch (with similar axon flares to healthy skin) suggests that the processes responsible for these observations are mediated centrally.

Our results also suggest that nonaffected areas of AD have altered itch response to repetitive painful and scratching stim-

uli; however, the magnitude of histamine-induced itch in these areas is much less than in lesional skin, as previously documented by Heyer *et al.*<sup>17</sup> and Ikoma *et al.*<sup>5</sup> Our results contrast with previous studies, which demonstrated that non-affected skin of AD responds similarly to healthy controls.<sup>7,15</sup> There are several possible explanations for this discrepancy. Firstly, we employed quantitative thermosensory testing with a continuous COVAS; in contrast, Ikoma *et al.* asked patients to rate the itch response at fixed times. In addition, this study employed repetitive stimuli vs. the single stimulus performed in previous studies. Thus, the current study may more accurately reflect the clinical condition in AD where patients scratch regularly. Previous studies used pinprick stimuli rather than scratching stimuli, which may differ in activation of mechanoreceptor A-fibres. Furthermore, our study used histamine-induced itch as a baseline while the previous studies had no such baseline.

In addition to central sensitization, there may also be a peripheral effect of noxious stimuli on histamine-induced itch in AD. It is well known that patients with AD itch and scratch in skin areas that have no visible lesional skin changes. A recent large study<sup>18</sup> demonstrated that itch intensity in patients with AD correlated with transepidermal water loss (TEWL), a measure of skin barrier function, in nonlesional skin of AD forearms. TEWL was significantly related to itch intensity but not to disease severity. The stratum corneum barrier function is known to be impaired throughout the body of patients with AD, not only in lesional skin; this defect may lead to a signalling mechanism by which skin nerve fibres in close proximity to the stratum corneum are chronically activated. Convincing evidence of peripheral sensitization in nonlesional skin of patients with AD emanates from studies demonstrating elevated inflammatory mediators as well as neurotrophins in nonlesional skin of patients with AD.<sup>19,20</sup> These mediators are known to induce neuronal sensitization in both pain and itch.<sup>21</sup>

No correlation was noted between itch and pain sensitivity in either lesional, nonlesional or healthy skin, the latter consistent with our previous study.<sup>4</sup> These results differ from a recent study in animal models which suggested that pain sensitivity is negatively correlated with itch sensitivity.<sup>22</sup> In humans, it appears that itch sensitivity is independent of pain sensitivity in both healthy individuals and in patients with AD. Although there are reports of a sex difference in pain perception,<sup>23,24</sup> our data do not show any gender difference in the perception of itch, pain and scratching as previously reported.<sup>2</sup> It is possible that our study was too small to detect any differences.

The present study does not explain why patients with AD frequently report through questionnaires that scratching and hot showers are the only means to reduce itch.<sup>2</sup> The desire to scratch may be related to the activation of brain areas that are associated with motivation and reward systems.<sup>25–29</sup> This may lead to the vicious itch-scratch cycle. The current study did not use harsh methods of scratching and the heat pain cycles were of short duration; therefore, it is possible that harsh

scratching, commonly observed in AD patients with excoriations and lichenification, as well as prolonged hot showers and painful stimuli, do temporarily inhibit itch. However, it is clear that these methods further damage the stratum corneum in the long run and augment the itch-scratch cycle.

In conclusion, the histamine-induced itch response to repetitive noxious stimuli and scratching is altered in AD. Although the current study does not allow us to identify the precise mechanisms and role of peripheral vs. central sensitization, both are suggested. Therapeutic approaches that inhibit nerve sensitization, such as those currently used for neuropathic pain, may have a role in the reduction of itch in AD. Furthermore, future studies addressing the effects of noxious stimuli on histamine-induced itch in other types of acute and chronic pruritic skin conditions will be of particular interest.

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