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Histamine-induced Itch and Alloknesis (Itchy Skin) in Atopic Eczema Patients and Controls

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Alloknesis ("itchy skin") after histamine iontophoresis was studied together with itch sensations and skin reactions in 19 atopic eczema patients and 20 controls at the forearm and at the scapular area. Compared to controls, atopic eczema patients showed significantly reduced alloknesis or total lack of it in the area around a skin site to which histamine had been iontophoretically applied, although histamine elicited itching in most patients. As previously demonstrated, patients with atopic eczema also developed significantly smaller flares. However, covariance analysis revealed that the smaller alloknesis areas in atopic patients were not statistically related to the smaller flares. Our results suggest that in atopic eczema a diminished responsiveness of primary afferent nerves to histamine is not compensated by a higher central nervous sensitivity reflected in more vivid alloknesis responses to histamine. Therefore, we conclude that histamine is probably not the key factor of the spontaneous itch experienced by patients with atopic eczema. ***Key words: itch sensation; neurophysiological mechanisms.***

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The phenomenon of "itchy skin" was first described by Bickford about 60 years ago (1) and defined as an area of skin where slight mechanical stimulation elicits itch. Itchy skin is experienced, for example, in the surroundings of an insect bite. Recently, LaMotte et al. introduced the term "alloknesis" (from the Greek, allos = other, knesis = itch) in parallel to the term "allodynia" which has been used for painful sensations elicited by gently touching or stroking the skin (2).

Alloknesis is explained by the excitation of itch-mediating central neurones through interneurones getting input from mechanoreceptor units (fast-conducting myelinated fibers). This input has to be gated by the polymodal unmyelinated C-fibers (slowly conducting fibers, mediating itch and pain sensations), activated by the local pruritogenic stimulus (3, 4). Since alloknesis, like allodynia, is probably mainly due to central nervous plasticity rather than changes in excitability of peripheral afferent nerve fibers (3, 4), it may provide insight into central nervous mechanisms. However, to our knowledge, no studies on alloknesis have hitherto been performed in patients suffering from itching dermatoses.

In this paper we report observations on the extension of itchy skin around sites of standardized histamine applications in patients suffering from atopic eczema (AE), compared to healthy subjects. By these experiments we tried to reevaluate the puzzling observation that AE patients suffering from itching dermatosis surprisingly show attenuated responsiveness to iontophoretical histamine application (5) and also to i.c. injected substance P (6).

MATERIAL AND METHODS

Experimental subjects

Experiments were performed between October 1992 and March 1993 in 5 male and 14 female patients, aged 14 to 49 years, (mean age 30 years), suffering from an acute exacerbation of AE. The individual history of atopy ranged from 1 to 42 years (mean 14.6 years). Family history of atopy was reported in 10 cases, and atopic symptoms other than AE were found in 12 cases (allergic rhinitis (9), allergic asthma (2), both allergic rhinitis and asthma (1)). The median serum IgE-level was 120 (range 37–3,990) U/ml. No patients with systemic corticoid or ACTH therapy in the previous 3 months were included. Therapy with antihistamines or other drugs influencing the skin blood flow was stopped 3 days prior to the investigation. Skin sites devoid of signs of inflammation were chosen for testing.

Twenty healthy volunteers, 12 females and 8 males, aged 18 to 35 years (mean age 26 years) served as control group. Neither these subjects nor their family members reported atopic symptoms. The drug exclusions for the patient group also applied to the controls.

Informed consent was obtained from all subjects, and the protocol of the study was approved by the local ethics committee.

Experimental procedure

Before the experiment, subjects rested for 15 min in a room kept at a temperature of 22°C. The tests were performed between 1 p.m. and 3 p.m. Histamine was iontophoretically applied by delivering a current of 1 mA for 20 s (= 20 mC) from an applicator (diameter 5 mm) following the same procedure as described in previous papers (5, 7). In each subject we applied histamine to two areas, the volar surface of the lower right or left arm and the back in the right or left regio scapularis. The time interval between the two tests was at least 20 min. Care was taken to select skin areas devoid of visible signs of inflammatory reactions.

Assessment of skin reactions to histamine

Areas of wheals and flares induced by histamine iontophoresis were assessed at 3–4 min intervals (3.5, 7.5, 11, 14, 17, 20, and 23 min after histamine stimulus) by drawing their borders on acetate sheets. For skin temperature measurement in the flare area an infrared thermometer was used ("Thermo-Hunter HR-1PL", Optec, Japan), which allows a contact free assessment of the skin surface temperature in small skin areas. Temperature was determined just before, and 0.5, 1, 3, 5, 7, 10.5, 13, 16, 19 and 22 min after histamine application.

Assessment of itch and alloknesis

Subjects were asked to express the intensity of their histamine induced itch sensations at intervals of 1 min on rating scales by assigning figures of 0–10. On this scale "0" was defined as "no itch sensation", "10" as "maximal imaginable itch sensation".

The area of alloknesis was obtained by gently stroking the surrounding skin with a soft brush. Starting at a distance of 8 cm from the site of histamine application the brush was slightly passed over the skin in centripetal direction. In this way the border of the itchy skin region was determined from 5 different directions. The points from where the skin felt itchy were marked and the 5 points were connected. The so determined area of alloknesis was transferred to acetate sheets. This test was performed 2, 4, 6, 8, 9.5, 12, 15, 18, 21, and 24 min after histamine iontophoresis.

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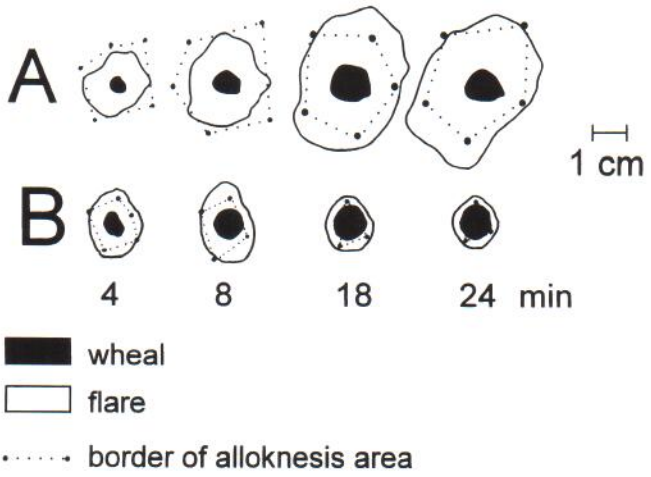

Fig. 1. Development of wheal, flare and alloknesis areas after examples of these reactions observed in a control subject (A) and in an AE patient (B) 4, 8, 18 and 24 min after the histamine stimulus at the regio scapularis.

Skin cooling

Since it is known that skin cooling attenuates itch sensations and alloknesis (8,9), the effect of cold stimuli on the itch sensations after histamine iontophoresis and on maintenance of alloknesis was also studied. To this purpose, we placed a cooling element (frozen sealed plastic water pack, size 10 × 10 cm) with a temperature of –6°C on the histamine-pretreated skin area for 10 s, starting exactly 8 min after histamine application.

Statistical evaluation

Data were organized in a spreadsheet (EXCEL®, Microsoft) and the STATISTICA® software package (Statsoft, Tulsa, OK, USA) was used for statistical evaluation. $p < 0.05$ was regarded as statistically significant.

RESULTS

Wheal and flare reactions

Wheals and flares developed slowly after the 20 s of histamine iontophoresis. On average, maximum wheal size on the back was reached after 17 min in control subjects (163 mm² ± 71) and after 14 min in AE patients (112 mm² ± 50). At the lower arm maximal wheal sizes were observed after about 20 min in controls (124 mm² ± 34) compared to 17 min in AE patients (98 mm² ± 38). Flares reached their maximal extension about 3 min later on the back, but before the wheal maximum on the lower arm. The differences in the temporal development of wheals and flares between patients and controls were statistically not significant. At an early stage, wheal sizes in control subjects and in AE patients were similar. Later on, after the cooling provocation, wheals reached a larger extension on the back of controls compared to AE patients ($p < 0.05$, ANOVA).

Flares on the back of control subjects were larger (maximum area at 17 min 2,260 mm² ± 720) than those of AE patients (maximum area at 11 min 1,457 mm² ± 979) throughout the observation period ($p < 0.01$, ANOVA). On the lower arm, control subjects developed larger flares only during the period after the cooling provocation (maximum area in controls at 17 min 1,739 mm² ± 499, in AE patients at 11 min 1,200 mm² ± 971), ($p < 0.01$, ANOVA). Examples of the development of wheals, flares and alloknesis areas in a control subject and in an AE patient are shown in Fig. 1.

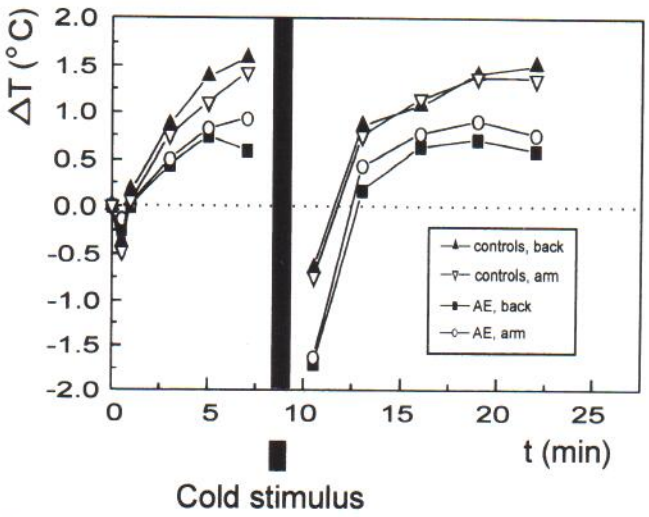

Fig. 2. Histamine-induced change of local skin temperature. Average of skin temperature, measured with an infrared thermometer in flare areas of AE patients and controls on the back and the lower arm. Cold stimulus was applied for 10 s after 8 min.

Local skin temperature

On average, histamine iontophoresis induced an increase of local skin temperature by up to 1.5°C ± 0.43 on the back and 1.4°C ± 0.52 on the lower arm in control subjects. In AE patients the respective increase in skin temperature was smaller, namely 0.7°C ± 0.56 on the back and 0.9°C ± 0.87 on the lower arm, on average. As shown in Fig. 2 the temperatures in flare regions of patients and controls were significantly different on the back at three observation times and on the lower arm immediately after the cooling provocation ($p < 0.01$, ANOVA).

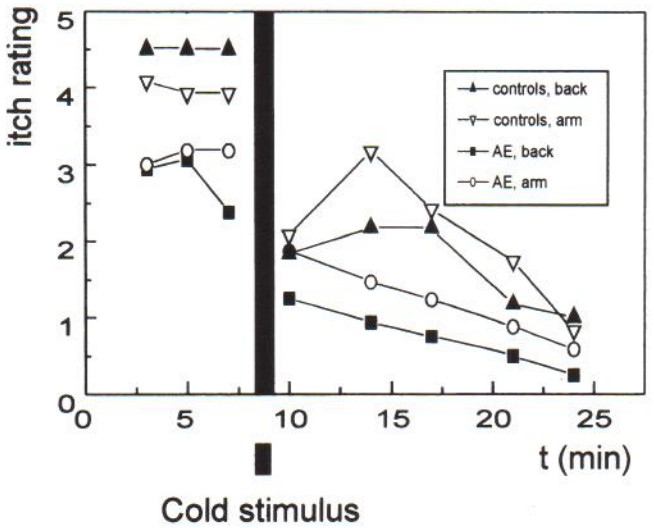

Fig. 3. Histamine-induced itch reactions. Average of itch intensity estimated on a category scale (0, 1, 2, ...10) in controls and AE patients on the back and the lower arm. Cold stimulus was applied for 10 s after 8 min.

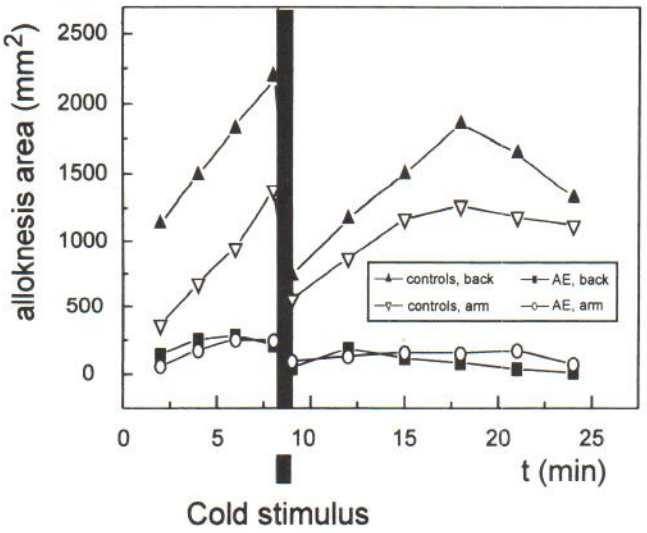

Fig. 4. Mechanically induced alloknesis areas. Average of alloknesis areas in controls and AE patients after histamine iontophoresis on the back and the lower arm. Cold stimulus was applied for 10 s after 8 min.

Itch sensations

After the end of iontophoresis itching usually developed; it often increased slowly during the first minutes.

The median maximal itch intensity on the back during the first 8 min was rated 5 by control subjects and 3 by AE patients. Respective values from histamine application to the lower arm were 4 in control subjects and 3 in AE patients. Immediately after cold provocation itching was suppressed in both controls and patients. After that it slowly recovered in controls, but not in patients (see Fig. 3). Itching was significantly stronger in controls on the back during the first 8 min ($p < 0.05$, Friedmann test) and on the lower arm shortly after cooling ($p < 0.05$).

Alloknesis

In healthy control subjects the area of alloknesis increased steadily during the first minutes after histamine application (see Fig. 1). In this group the areas of alloknesis were significantly larger on the back (maximum at 8 min 2,365 mm^2 ± 1,061) compared to the lower arm (maximum at 8 min 1,379 mm^2 ± 342) during the first 8 min ($p < 0.05$, ANOVA), whereas the smaller alloknesis areas in AE patients were similar at both locations (on the back: maximum at 6 min 280 mm^2 ± 568) compared to the lower arm: maximum at 8 min 251 mm^2 ± 360). Cooling provocation induced shrinking of alloknesis areas. After that they increased again in controls and almost regained the precooling size 10 min later (see Fig. 4). During the whole observation period control subjects exhibited much larger alloknesis areas than AE patients on both test sites ($p < 0.05$, ANOVA).

All but one of the control subjects but only 6 of 19 AE patients experienced alloknesis after histamine application to the back. At the lower arm 10 of the 19 AE patients did not report alloknesis compared to one control subject.

Alloknesis and flare sizes

Generally, sizes of alloknesis areas were similar to flare areas. In the control group their mean extension was 92–117% of the simultaneously measured flare areas at both testing sites at all observation times, apart from those immediately after cooling when alloknesis areas were markedly smaller than flare sizes. However, it has to be noted that the borders of the visible flare and of the alloknesis were generally not identical (see Fig. 1). Surprisingly, there was no significant correlation in the control group between flare and alloknesis sizes at any of the observation times, either when data from each application site were regarded separately, or when data from both sites were pooled. The same lack of correlation between flare and alloknesis sizes was observed in the AE patients and in pooled data.

In those AE patients who reported alloknesis, the areas were rather variable but tended to be smaller than flare areas. Median values were between 15 and 50% of the flare areas at most observation times.

An analysis of covariance (ANCOVA) with a repeated measurement design was employed for testing the impact of the flare sizes on alloknesis areas. In this analysis the dependent variable was the area of alloknesis. The independent factors were (1) "application site" (back or lower arm) and (2) "group" (AE patients vs. controls). (3) The measurements before cold provokation were included (repeated measurements 1–4). The covariate was the flare area 7 min after iontophoresis. Only AE patients who experienced alloknesis were included in the analysis. In this ANCOVA the factors (2) AE patients vs controls ($p = 0.002$) and (3) test repetition ($p = 0.000$) were significant. The factor (1) application site was not significant ($p = 0.162$). Most interesting, the covariate "size of flare" had no significant impact ($p = 0.65$). Including the size of the flare at another observation time in the analysis did not change the result.

The effects of cooling the skin

Application of the cold pack 8 min after histamine iontophoresis apparently did not impede further increases of wheal and flare sizes. There were no signs of shrinking wheals and flares during cooling. Not surprisingly, the local skin temperature was lowered immediately after cooling. Temperature recovered more quickly in control subjects than in AE patients (Fig. 2). In both groups it reached precooling values about 10 min after the cold provocation.

Itch sensations were markedly reduced after cooling in both groups of subjects. However, only in control subjects did itch intensity increase again some minutes afterwards (Fig. 3). Alloknesis areas were also markedly smaller after the cold stimulus. Again, during the first minutes after the cooling provocation alloknesis areas expanded only in healthy control subjects, but not in AE patients. In controls 3 min after cooling, the mean size of alloknesis areas was about 65% of the flare areas and 5 min later alloknesis had reached again approximately flare size, on average. In AE patients such a clear relationship was not observed.

Though both intensity of itching and alloknesis areas were diminished immediately after cooling, the correlation coefficients between the two parameters were low in that period (4

min after cooling: $r = 0.24$ in controls and $r = 0.34$ in AE patients, n.s.).

DISCUSSION

In previous studies (5, 6) we have hypothesized that AE patients might show a "downregulation" of cutaneous histamine receptors on different target structures, as a consequence of increased skin levels of histamine (10) and enhanced release of histamine from basophils (11) in AE. The unmyelinated polymodal afferent C-fibers responsible for the itch sensation seem to be desensitized to histamine. Alternatively, an increased histaminase activity can be discussed (12), leading eventually to a lower level of histamine acting on the target receptors in spite of the increased release.

Our present findings of reduced itch sensation and flare sizes after histamine application in AE confirm our former results of diminished itch sensation in AE patients, not only after iontophoretical histamine application (5) but also after i.c. injections of substance P (6), known to release histamine from cutaneous mast cells (13). A diminished rise of local skin temperature after histamine stimulus in AE patients was observed in parallel to smaller flare areas. Beside reduced erythematous reactions after histamine, we have also previously demonstrated a smaller increase of local skin blood flow by laser Doppler flowmetry in AE patients compared to healthy controls (5). The steeper fall in local temperature after the cold stimulus measured in AE patients might reflect their tendency to vasoconstriction reported in various studies (14, 15).

Other authors have also reported decreased histamine and substance P induced vasoreactions in AE, but no significantly diminished itch reactions (16, 17). The varying results with itch sensations may be related to the inherent variability of subjective reports. Therefore in the present study we employed another parameter of the sensitivity of itch-mediating nervous pathways, namely the extension of alloknesis, or "itchy skin" in the surroundings of a skin area in which histamine was employed.

Alloknesis or "itchy skin" has been explained by the excitation of itch-mediating central neurons through interneurons receiving input from low-threshold, fast-conducting mechanoreceptor units when gated by input from itch-mediating C-fibers (3, 4), by analogy with the explanation of allodynia, which has been attributed to the excitation of pain-mediating central projection neurons by input from fast conducting mechanoreceptor units gated by ongoing input from unmyelinated nociceptors (3, 18). This interpretation is supported by experiments utilizing differential ischaemic block of A-fibers (1).

It is striking that in healthy subjects areas of alloknesis and flare areas are very similar (see Fig.1). The smaller alloknesis areas in AE patients found in this study could therefore be a side effect of the smaller flares. However, analysis of covariance revealed that variations in flare areas were statistically by no means closely related to the size of alloknesis areas. This result indicates that the two areas are only in the same order of magnitude but not closely associated.

Since alloknesis is probably related to the excitability state of central itch-mediating pathways, this new finding indicates that the diminished peripheral responsiveness of AE patients to histamine application is not compensated by central sensitization.

Probably histamine is not the key factor of the spontaneous itch experienced by AE patients. This notion is supported by the finding that antihistamines could not relieve pruritus better than placebo in AE (19) and that mast cell degranulation inhibitors could not improve pruritus in AE (20).

Spontaneous itching is the key symptom in AE. One may hypothesize that, beside the involvement of peripheral mechanisms (e.g. other, not yet defined transmitters), a central nervous alteration might account for the well-known unbearable pruritus attacks in AE. To test this hypothesis it would be interesting if proneness to itch reactions and also to alloknesis after application of other stimuli than histamine is increased in AE. One indication in this direction is probably provided by the work of Wahlgren et al. (17), who studied mechanically induced itching in AE patients by using wool fibers of a particular diameter. He found significantly different reactions in quality and quantity in AE compared to controls. AE patients reported a pure itch without a pricking sensation and they also perceived stronger itch sensations.

Further studies including testing of alloknesis after various kinds of itch provocation in AE patients may shed light on central components in pathological itching.

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