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Patients' Perception of Itch Induced by Histamine, Compound 48/80 and Wool Fibres in Atopic Dermatitis

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Itch and flare responses were investigated in 32 patients with atopic dermatitis (AD) and in 32 healthy controls. Itch was induced chemically by intradermal injections of histamine (1, 3.3, 10 and 100 μg/ml) and compound 48/80 (10 μg/ml) into non-lesional skin and mechanically by wearing a woollen sweater. Continuous recording of itch intensity allowed the calculation of itch duration (ID), maximal itch intensity (Imax) and a "total itch index" (Tii).

The itch responses were significantly increased in AD patients compared with controls for wool fibres and one of the histamine concentrations (10 μg/ml), but not for the remaining three histamine concentrations or compound 48/80. Conversely, the flare response was significantly smaller in AD patients than in controls for the two strongest histamine solutions and compound 48/80. Significant dose-response relationships were found between histamine concentration and each of ID, Imax, Tii and flare in both patients and controls. The slope of the flare-regression line was significantly steeper in controls than in AD patients, whereas the slopes of the itch-regression lines did not differ significantly between the two groups, i.e. their ability to discriminate between weak and strong histamine concentrations did not differ significantly. No increased skin mast cell releasability in vivo to compound 48/80 was shown in AD patients compared with controls. The itch and flare responses of AD patients did not correlate significantly with clinical itch intensity, eczema score or serum IgE level. ***Key words: Pruritus; Flare; Histamine release.***

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The pathogenesis of itch in atopic dermatitis (AD) is still unknown. According to Rajka (1, 2) two factors are of importance: 1) various immunological or non-immunological stimuli provoking pruritus, and 2) an increased itch sensitivity with e.g. reduced itch threshold (i.e. the lowest concentration of a solution provoking itch) or prolonged itch duration for pruritic stimuli.

Using intradermal injections of histamine, Cormia determined the itch threshold in patients with different pruritic dermatoses (3). The threshold was lower in involved than in uninvolved skin, but only one case of AD was included in the investigation. Arthur & Shelley (4) found decreased itch thresholds for intradermally injected trypsin and a prolonged itch duration for mucuna pruriens (cowhage) spicules inserted into lesional skin of the antecubital fossa in 5 AD patients, compared with healthy controls. With intradermal injections of trypsin, Rajka showed that the duration of itch was prolonged (> 2 min) significantly more often in involved (5) and uninvolved skin (6) in 25 and 20 AD patients, respectively, compared with subjects with various other eczematous lesions or psoriasis. Moreover, itch duration in involved skin seemed to discriminate better between the AD group and eczema-psoriasis groups than itch threshold did (5). However, in a study of itch duration in involved and uninvolved skin in 100 AD patients and 115 non-AD patients, Harnack (7) concluded that the "trypsin test" was not decisive in the differential diagnosis of AD.

Recently, it has been shown that itch intensity in experimentally-induced pruritus in healthy subjects can be validly rated using magnitude estimation (8), a fixed-point non-verbal scale or a visual analogue scale (VAS)(9). Heyer et al. (10) used histamine iontophoresis at 6 different current intensities in non-lesional skin in 27 AD patients and 20 healthy controls and measured the itch intensity. They showed that the slope of the dose-response curve was significantly steeper in the controls than in the AD patients; thus, the controls perceived a significantly higher itch intensity to the strongest histamine stimulus than did the AD subjects. The latter were also, unlike the controls, unable to distinguish between weak and strong histamine stimuli. This report of reduced itch sensitivity is in contrast to previous findings of decreased itch threshold and

prolonged itch duration in experimentally-induced pruritus in AD.

The aim of our study was to investigate further the perception of experimentally-induced itch in AD and healthy controls, and to correlate the experimental findings with clinical data.

MATERIAL AND METHODS

Subjects

Thirty-two patients with persistent AD (median age 24 years, age range 18–41 years) and 32 healthy controls (median age 22, age range 18–41 years) participated in the study. Each group consisted of 15 men and 17 women. The investigation was performed by the same investigators, in the period February–April, and was approved by our Ethics Committee.

The AD patients, who all fulfilled the criteria of Hanifin & Rajka (11), were recruited from those who had attended our department over the previous 6 months. Median age at onset of AD was 6 months (range 3 months–25 years). In all patients, itching had persisted longer than the previous 12 months. The majority, 22/32 (69%) had a past or present history of respiratory atopy (asthma in 1/32, rhinoconjunctivitis in 11/32 and both in 10/32), but none required regular pharmacotherapy because of this. The mean serum IgE level (± SD) was 1563 ± 2500 kU/l (range 2–8800 kU/l), and an increased level (> 263 kU/l for those aged between 18 and 20, > 122 kU/l for those above 20) was found in 19/32 (59 %). White dermographism was found in 23/32 (72%). The extension and intensity of AD were scored according to a "twenty-area severity chart" (12), where the severity of eczema in each of 20 areas was assessed on a 0–3 scale (no, mild, moderate or severe), giving a total score of 0–60. The mean eczema score (± SD) was 9.1 ± 7.8 (range 1–30). Prior to the induction of experimental itch, the AD patients rated their "overall" intensity of clinical itch for the previous 24 h on a 100-mm visual analogue scale (VAS) form. The left and right end points of the VAS were marked "no itch" (0 mm) and "maximal itch" (100 mm), respectively. The patients' mean clinical itch intensity (± SD) for the previous 24 h was 41.1 ± 30.0 mm.

Exclusion criteria were age below 18 years, pregnancy or lactation, present history of any other disease than atopy, present eczema on the lateral aspect of the upper arms (test area for injections), acute infections, internal pharmacotherapy during the previous 7 days, internal corticosteroids for the previous 3 months, topical semi-potent/potent corticosteroids on the lateral aspect of the upper arms or UV therapy/sunbeds for the previous month, and topical hydrocortisone on the lateral aspect of the upper arms for the previous week.

The healthy controls were recruited among hospital staff and students. The controls were not allowed to have any past or present history of atopy (including parents', brothers' and sisters'), skin disease or present pruritus. Otherwise the exclusion criteria were identical to those of the AD patients. Serum IgE was not analysed.

Induction of itch

Itch was induced by chemical (injections) and mechanical (wool) stimuli. Four concentrations (1.0, 3.3, 10 and 100 μg/ml) of histamine hydrochloride (ACO Läkemedel AB, Sweden) and one concentration (10 μg/ml) of the histamine-liberator compound 48/80 were made by dilution with sterile pyrogen-free physiological saline containing 10 % Sörensen phosphate buffer (Na_2HPO_4+KH_2PO_4, 67 mM), pH 7.40. Buffered saline also served as control. Using a double-blind technique, 10 μl of each solution was injected intradermally by the same investigator into non-lesional skin of the lateral aspect of the upper arms. The order of the six different injections was random, odd numbers being given on the left upper arm and even numbers on the right upper arm.

After completion of the injections, a knitted woollen sweater with long sleeves was put on and worn as a mechanical itch inducer. The fibre diameter was determined according to international standards (ISO 137–75) and for 140 randomly chosen wool fibres the mean value (± SD) was 33.4 ± 7.9 μm (i.e. fibre thickness medium to coarse).

Recording of experimental itch

The intensity and duration of the experimentally-induced itch were monitored continuously for up to 15 min after each injection and for 5 min with the woollen sweater, using a linear potentiometer equipped with a 100-mm VAS. The potentiometer lever, sliding along the VAS, controlled the position of a pen on a plotter out of sight of the subject.

Table I. *Itch duration (ID)*

Mean value ± SD (sec). Recording time for wool fibres 5 min, for all other agents up to 15 min. P value denotes a significant difference between patients with atopic dermatitis (n = 32, except for wool fibres, where n = 30) and healthy control subjects (n = 32). NS = not significant.

Agents	Atopic dermatitis	Control subjects	P
Saline	20.8±55.1	17.7±50.2	NS
Histamine 1 μg/ml	60.6±70.2	51.3±79.2	NS
Histamine 3.3 μg/ml	130 ± 148	109 ± 110	NS
Histamine 10 μg/ml	234 ± 204	141 ± 129	<0.05
Histamine 100 μg/ml	366 ± 263	311 ± 262	NS
Compound 48/80 10 μg/ml	200 ± 159	190 ± 170	NS
Wool fibres	178 ± 129	77.8±112	<0.01

Table II. *Maximal itch intensity (Imax)*

Mean value ± SD (mm). P value denotes a significant difference between patients with atopic dermatitis (n = 32, except for wool fibres, where n = 31) and healthy control subjects (n = 32). NS = not significant.

Agent	Atopic dermatitis	Control subjects	P
Saline	2.0± 5.0	1.7± 4.7	NS
Histamine 1 μg/ml	13.1±15.4	6.9±12.0	NS
Histamine 3.3 μg/ml	21.2±23.1	19.9±26.6	NS
Histamine 10 μg/ml	39.8±29.8	23.4±24.5	<0.05
Histamine 100 μg/ml	49.7±30.1	42.7±28.3	NS
Compound 48/80 10 μg/ml	35.7±28.0	28.9±25.7	NS
Wool fibres	23.7±23.8	11.4±17.8	<0.05

The end points were marked as in the VAS forms described above. The time interval between injection and start/stop of itch was recorded as well as the perceived itch intensity. This allowed the calculation of itch duration (ID, sec), peak value of itch (Imax, 0–100 mm), and a "total itch index" (Tii=area under the curve on the plot, mm^2), reflecting both intensity and duration of itch. In the cases where wool provoked itch, the subjects were asked to state whether or not the itching was accompanied by a pricking sensation.

Recording of flare

Five min after the injection, the flare reaction was outlined with a marking pen on the skin and traced onto transparent plastic film from which the area (mm^2) was calculated using a planimeter (model 317, Gebrüder Haff GmbH, Pfronten, FRG).

Statistical methods

The chi-square test was used for analysing frequency of itch induction and qualitity of itch. For ID, Imax, Tii and flare both the non-parametrical Mann-Whitney U test (two-tailed) and the parametrical Student t test (two-tailed) were used for comparisons between the AD patients and the controls. The two tests gave very similar results, and those presented are based on Mann-Whitney's U test. An overall test across all four histamine doses was also performed by means of a repeated-measurement model allowing for interaction between dose level and patient group. Each subject's dose-response curve between histamine concentration and each of ID, Imax, Tii and flare was computed using linear regression analysis (model: $y = \alpha + \beta \cdot \log x + \varepsilon$). The intercepts ($\alpha$) and slopes ($\beta$) of the patients and controls were compared using Student's t test. Multiple regression analysis was performed to check for the impact of age and sex on histamine-induced itch and flare.

RESULTS

Experimental itch responses

The intradermal injections were given to all subjects. One of the patients with AD refused to put on the woollen sweater and another could not stand wearing it for more than 85 sec (perceiving Imax = 96 mm).

The different pruritic stimuli did not induce an itch response in significantly more AD patients than in healthy controls, although the wool fibres showed a tendency to do so (23/31 vs 16/32). The quality of the itch sensation provoked by wool fibres differed significantly ($p < 0.01$) between the two groups. Thus, 16/23 (70%) AD patients responding to wool,

Table III. *Total itch index (Tii)*

Mean value ± SD (mm^2). Recording time for wool fibres 5 min, for all other agents up to 15 min. P value denotes a significant difference between patients with atopic dermatitis (n = 32, except for wool fibres, where n = 30) and healthy control subjects (n = 32). NS = not significant.

Agent	Atopic dermatitis	Control subjects	P
Saline	206± 794	181± 598	NS
Histamine 1 μg/ml	791± 1083	730± 1705	NS
Histamine 3.3 μg/ml	2119± 2984	2569± 5033	NS
Histamine 10 μg/ml	7435±10959	3065± 4636	<0.05
Histamine 100 μg/ml	12588±17872	9206±10003	NS
Compound 48/80 10 μg/ml	4689± 5089	4489± 6454	NS
Wool fibres	3630± 3902	1329± 3048	<0.01

Table IV. *Intercepts and slopes from linear regression analysis. Dose-response relationships between histamine concentration and itch or flare responses in 32 patients with atopic dermatitis (AD) and 32 healthy controls (CO) [model: $y = \alpha + \beta \cdot logx + \varepsilon$].*

Mean values of the 32 estimated intercepts (α) and slopes (β) for each group. Standard errors for the slopes in brackets. P value denotes a significant difference between the two groups. NS = not significant.

Variables	Intercepts (α)			Slopes (β)		
	AD	CO	P	AD	CO	P
Itch duration (ID)	60.8	39.5	NS	156 (23.9)	129 (21.2)	NS
Maximal itch intensity (Imax)	14.3	8.1	NS	19 (2.6)	17 (2.2)	NS
Total itch index (Tii)	254	204	NS	6229 (1699)	4193 (817)	NS
Flare	134	268	NS	518 (48.8)	691 (56.0)	<0.05

but only 3/16 (19%) controls responding to wool, felt pure itch without a pricking sensation.

The experimental itch responses are shown in Tables I–III. The ID, Imax and Tii for histamine 10 μg/ml and for wool fibres were significantly higher in the AD patients than in the controls. For histamine, the repeated-measurement model did not show significant differences between the two groups ($p = 0.14$, 0.10 and 0.21 for ID, Imax and Tii, respectively).

AD patients and controls both showed significant dose-response relationships ($p < 0.001$) between histamine concentration and ID, Imax or Tii (Figs. 1(a)-(c), respectively). The intercepts (α) and slopes (β) did not differ significantly between the two groups of subjects, as shown in Table IV. The slopes for ID, Imax and Tii show that both AD patients and controls were able to discriminate between weak and strong histamine stimuli and that the discriminative ability for these histamine-induced itch responses did not differ significantly between the two groups.

The sex and age of the subjects had no significant influence on the values of ID, Imax or Tii, although a tendency to reduced values was found with increasing age.

Experimental flare responses

Saline, histamine and compound 48/80 did not induce flare reactions in significantly more patients with AD than in control subjects.

The flare responses are shown in Table V. The two strongest histamine concentrations (10 and 100 μg/ml) and compound 48/80 induced significantly smaller flares in the AD group than in the control group. For histamine, the repeated-measurement model also showed a significant difference between the two groups ($p < 0.05$).

AD patients and controls both showed a significant dose-response relationship ($p < 0.001$) between histamine concentration and flare response (Fig. 1d). The slope (ß) of the flare-regression line was significantly steeper ($p < 0.05$) in the controls than in the AD patients (Table IV).

The flare reactions induced by histamine and compound 48/80 were significantly larger ($p < 0.01$) in women than men in both the AD and the control

Table V. *Flare responses*

Mean value ± SD (mm^2). P value denotes a significant difference between patients with atopic dermatitis (n = 32) and healthy control subjects (n = 32). NS = not significant.

Agents	Atopic dermatitis	Control subjects	P
Saline	34.8±108	20.4±53.0	NS
Histamine 1 μg/ml	194±333	295±358	NS
Histamine 3.3 μg/ml	361±475	634±586	NS
Histamine 10 μg/ml	593±627	892±507	<0.05
Histamine 100 μg/ml	1211±737	1679±753	<0.01
Compound 48/80 10 μg/ml	556±591	1040±806	<0.01

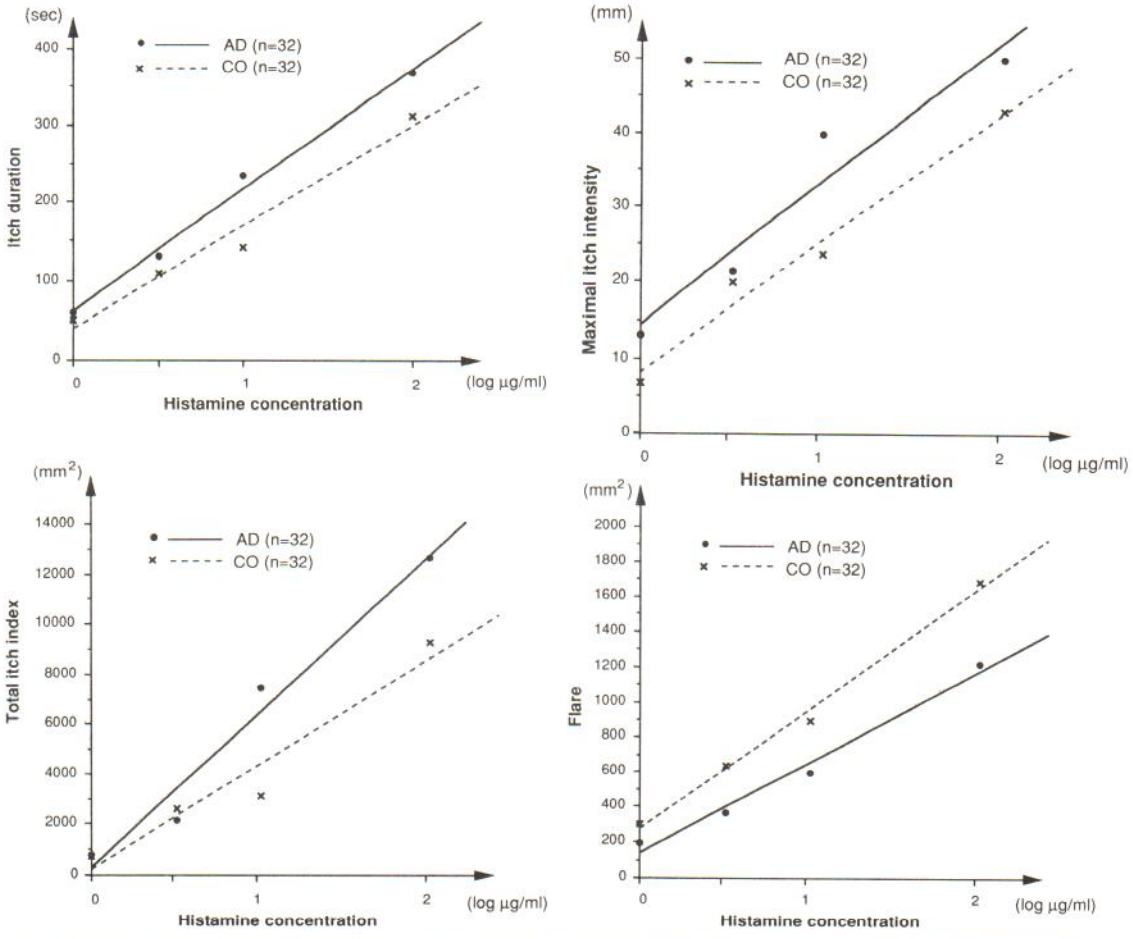

Fig. 1. Estimated regression lines (model: $y = \alpha + \beta \cdot \log x + \varepsilon$) showing the dose-response relationships between histamine concentration and each of *(a)* itch duration (ID), *(b)* maximal itch intensity (Imax), *(c)* total itch index (Tii) and *(d)* flare response, respectively, in 32 patients with atopic dermatitis (AD; ——) and in 32 healthy controls (CO; - - - -).

groups. Age did not influence the flare responses significantly.

Correlations

No significant correlations were shown between the Tii for wool and the Tii for any of the injections given. In the AD patients, neither the Tii (injections, wool), nor the flare (injections), correlated significantly with the clinical itch intensity, or eczema score, or serum IgE_c

DISCUSSION

The most appropriate method to induce and study itch in patients with AD would probably be to use the pathogenic pruritic mediator(s) of this disease, but this substance or these substances are still undentified. Histamine was chosen, being the most thoroughly studied pruritic agent, although we do not consider it of major importance in the pathogenesis of itch in AD (13). Compound 48/80 was included because of its ability to activate mast cells for mediator release, thereby elucidating skin mast cell releasability in vivo. Wool fibres were chosen for two reasons: they provoke pruritus by mechanical stimulation, and this woollen-provoked itch is of clinical significance to most AD patients (11, 14).

For wool fibres, the quality of the perceived itch sensation differed significantly between the AD group and controls, i.e. more of the former felt a "pure" itch, which is in agreement with previous reports of an increased itch sensitivity in AD. Wool fibres also induced significantly more pronounced itch responses in AD patients than in controls. For

histamine, the itch responses were significantly increased in the AD group for one of the concentrations (10 μg/ml), but not for the other three; although a tendency towards a difference was seen for the latter. With more subjects, significant differences might have been achieved. For example, for Tii induced by histamine 100 μg/ml, we would have needed about 150 subjects per group for the observed difference to be significant at the 5% level, assuming a standard deviation of 15000 in each group.

The intercepts and slopes of the histamine-induced dose-response relationships for itch did not differ significantly between patients and controls, showing that their ability to discriminate between different histamine concentrations did not differ. This is in conflict with the data of Heyer et al. (10), who found that only healthy controls, but not AD patients, could discriminate between weak and strong histamine stimuli. An explanation for the discrepancy between our findings may be that Heyer et al. used iontophoresis to administer histamine. As the skin barrier in AD is defective also in normal-looking skin (15), it may be difficult to administer a well-defined histamine dose close to the epidermodermal junction, where the itch response is thought to be maximal (16).

A somewhat unexpected finding in the AD patients was that, in general, the Imax for the woollen sweater was less than the Imax for injections of histamine 10 or 100 μg/ml, i.e. a pruritic stimulus at a single point was perceived as more intense than pruritic stimulation over a larger area. Furthermore, the severity of eczema did not correlate significantly with the wool-induced itch responses, e.g. the AD patient with the highest Imax to wool (96 mm) was in fact the patient with the lowest eczema score. Some AD patients reported that if they sat absolutely still, breathing very calmly, they could minimize the itch intensity induced by wool; and such factors may contribute to the lack of correlation between itch and eczema score. On the other hand, the itch responses to the injections were not more pronounced in patients with severe eczema.

The non-immunological (non-IgE-dependent) mast-cell stimulator compound 48/80 induced equal itch responses in AD patients and controls but significantly smaller flare reactions in AD patients than in controls. Several investigators have shown an increased histamine releasability in vitro from basophilic granulocytes of AD patients (e.g. 17). Our present study does not indicate a significantly increased skin mast cell releasability to non-immunological stimuli in vivo in non-lesional skin in AD patients, as the compound 48/80-induced itch and flare responses were not increased in the AD group.

The phenomenon of diminished flare responses in AD patients is well known (e.g. 18), but its cause is unknown, as is the reason for significantly different flare sizes in men and women in our study. The latter emphasizes the importance of sex-matching, when comparing flare responses between different groups. The flare reaction depends on an axon reflex with the putative release of mediators from peptidergic nerve endings, such as substance P and probably also other neuropeptides, stimulating mast cell degranulation as well as having direct vascular effects, producing vasodilatation (19, 20). Tachyphylaxis to histamine due to elevated histamine levels in atopic skin seems less probable, as histamine-induced itch responses were not lower in AD patients than in controls. The possible mechanism for the diminished flare in AD patients could be a defect at any level in the cascade of interactions between peptidergic mediator release, mast cells and blood vessels. When neuropeptides such as substance P or neurotensin are injected intradermally, they provoke a reduced flare but an equal itch response in AD patients compared with non-atopic controls (21). In other words, the peptide-induced responses are similar to those induced by histamine in our present investigation. The dermal skin vessels in AD are thought to have an increased α-adrenoceptor sensitivity, and a local vasoconstriction in the dermal blood vessels may explain the diminished flare response in AD subjects (e.g. 18, 22).

In conclusion, our study shows significantly increased itch responses to wool fibres and to one of four histamine concentrations in AD patients compared with healthy controls. The ability to discriminate between weak and strong histamine concentrations did not differ significantly between patients and controls. The flare responses induced by histamine and compound 48/80 were significantly smaller in patients than in controls. No increased non-immunological skin mast cell releasability was shown in vivo, as compound 48/80-induced itch or flare reactions were not increased in AD patients compared with controls. The experimental itch and flare responses of the AD patients did not correlate significantly with clinical itch intensity, eczema score or serum IgE level.

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