

Histamine and Cutaneous Nociception: Histamine-induced Responses in Patients with Atopic Eczema, Psoriasis and Urticaria

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Having observed altered itch and flare reactions after histamine application in patients with atopic eczema, we tried to determine these reactions in patients with urticaria and psoriasis. We investigated 16 healthy non-atopic subjects, 16 atopics in an eczema-free interval, 16 with acute atopic eczema, 16 with urticaria and 16 with psoriasis. Histamine was iontophoretically applied. The resulting sensations were rated on a visual analogue scale. Flare areas were measured 6 min after stimulation. Itch ratings of urticaria and psoriasis patients did not differ significantly from controls, whereas both atopic groups, regardless of acute or symptom-free state, reported significantly reduced intensity of itching. Flares were significantly diminished in all subjects with acute skin disease (psoriasis, urticaria and atopic eczema), regardless of diagnosis. However, flares were "normal" in symptom-free atopics and were not significantly different from controls. In conclusion, all "acute" patients showed a diminished axon-reflex function, possibly due to a downregulation of C-fiber responsiveness to histamine or an increased turnover rate of inflammatory mediators. Both atopic groups reported weaker itching, suggesting altered central nervous processing of itch.

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In patients with atopic eczema (AE), reduced flare reactions after intracutaneous application of histamine or substance P, known to release histamine from cutaneous mast cells, have been reported by several investigators (1–5). The reason for the diminished histamine-induced axon-reflex erythema could be tachyphylaxis due to increased levels of histamine and other inflammatory mediators, including neuropeptides, which indeed have been found to be increased in atopic skin (6, 7). The possibility of an increased enzymatic degrading process with an increased turnover rate of these mediators, including histamine, also has to be considered.

Although severe pruritus is one of the main symptoms of AE, we observed weaker itching after intracutaneous histamine application in these patients compared to healthy controls (1, 8). Intracutaneous substance P injection similarly evoked diminished pruritogenic histamine reactions in patients with AE (2). Recently we reported altered histamine sensations but unimpaired cutaneous vascular reactions in symptom-free atopic individuals (8).

In the present study we tried to determine whether the diminished cutaneous reactions after histamine iontophoresis in patients with AE are typical of this skin disease or whether they are an unspecific finding also existing in other inflammatory skin diseases. Therefore, we studied cutaneous histamine

reactivity in patients with other partly itching skin diseases. We included patients suffering from psoriasis (PSO) and from chronic urticaria (URT), who in comparison to patients with AE were in an acute period of their disease, as well as AE patients in an eczema-free interval. Healthy, non-atopic volunteers served as controls.

MATERIAL AND METHODS

Subjects

The study was performed on 80 individuals, forming five separate groups:

- 16 healthy volunteers (10 females and 6 males, age 23–46 years, average age 28) who served as controls.
- 16 patients with AE who were in an eczema-free interval (10 females, 6 males, age 20–37 years, average age 26) (=AE1).
- 16 patients with acute AE (11 females, 5 males, age 22–42 years, average age 27) (=AE2).
- 16 patients with PSO (8 males, 8 females, age 26–49 years, average age 33) (=PSO).
- 16 patients with chronic URT (10 females, 6 males, age 21–39 years, average age 26) (=URT).

The study was conducted between November and February. All subjects were of Caucasian origin. At the time of the experiment none of the subjects except those from the AE group had any atopic symptoms (AE, allergic rhinitis or asthma) or suffered from neurological, vascular diseases or dermatoses other than PSO or URT.

None of the volunteers were taking any drugs regularly with the exception of short-acting antihistamines, which were stopped at least 5 days prior to the experiment.

One group of patients with AE suffered from an acute outbreak of their disease during our study and all of them were treated as in-patients. The other group consisted of patients with AE who were free of AE during the experimental period. Atopic symptoms other than eczema were found in 24 of the 32 patients: 18 reported allergic rhinitis, 4 reported allergic asthma and 2 reported both allergic asthma and allergic rhinitis. The diagnosis of AE was established by physical examination and the patient's personal history, using the criteria of Hanifin & Rajka (9).

The URT patients participating in the study had shown chronic symptoms for at least 9 months prior to the study. Eleven of the 16 patients had had almost daily urticarial symptoms during the last weeks, so far of unknown origin. Three of these 11 patients had developed Quincke edema in the past. The other 5 patients reported URT after exercises, showing typical eruptions of cholinergic URT after exposition. All these patients stayed in the clinic for diagnostic procedure and had not yet received any specific treatment for their disease.

All PSO patients (all with typical PSO vulgaris) had had their disease for more than 1 year and were treated because of the acuity of their dermatosis as in-patients at the time of the study. They were similarly treated with topical application of tar, calcipotriol and/or cignolin. No topical steroid treatment or UV therapy was allowed.

Study design

After having given their informed consent the volunteers were examined by the same physician. Skin sites devoid of inflammation were chosen for testing and these areas were excluded from topical treatment. Tests were performed between 9 a.m. and 12 a.m. Room temperature was kept constant between 20°C and 22°C. The area to be tested was the left and right volar surface of the forearm.

Histamine iontophoresis

Histamine was applied to the forearm skin by iontophoresis, as previously described (1, 8). Histamine dihydrochloride (1%), (Sigma Deisenhofen, Germany) was dissolved in a gel of methylcellulose in distilled water and was placed in the cavity of an acrylic applicator having a diameter of 5 mm and a volume of 50 µl. A silver-silver chloride electrode in this applicator served for current delivery; another electrode (3 × 3 cm) was fixed on the forearm at about 10 cm distance from the first electrode and served as a reference. A constant current of 1 mA was applied from an isolated stimulator (WPI 305B, New Haven, CT, USA) for 10 s. As a control, 2.5% methylcellulose without histamine was iontophoretically applied.

Sensory rating

Fifteen seconds after termination of the iontophoresis, the volunteers started with the ratings of the intensity of the stimulus-induced itch. Ratings were given at 15-s intervals for 5 min. The left end of the scale of 10 cm was defined as "no itching", the right end as "maximal imaginable itching". The subjects had to mark the scale according to the actual intensity of itching.

Flare responses

Flare areas were outlined on translucent paper 6 min after the onset of iontophoresis for planimetric analysis.

Statistics

The area under the curve (AUC) of itch ratings was determined for each volunteer. Homogeneity of variance could not be confirmed in the five groups for the raw AUC-values ($p < 0.05$, Bartlett-Box test). After square root transformation variance homogeneity ($p > 0.9$, Bartlett-Box test) and normal distribution ($p > 0.3$, Kolmogoroff Smirnov test) could be confirmed. The flare reactions could be assumed to be normally distributed with equal variances ($p > 0.7$, Bartlett-Box test, $p > 0.4$ Kolmogoroff Smirnov test). Comparisons between the five groups were performed using one-way analysis of variance. Testing in pairs was performed with Scheffé correction. The age of the volunteers was compared using the Kruskal-Wallis test. All calculations were performed using SPSSWIN®.

RESULTS

The average age was 30.09 ± 9.85 ($n = 80$, mean \pm SD), spread across the five groups ($p > 0.4$, Kruskal-Wallis-test). During iontophoresis, the volunteers described the sensation induced by the current as slightly "pricking/burning". This sensation disappeared immediately after termination of the iontophoresis and was not continued for the data evaluation.

Control iontophoresis

Iontophoretically applied NaCl in methylcellulose induced merely weak sensations in most individuals. No differences between volunteers of the five groups were observed ($p > 0.5$, oneway-ANOVA). Flare reactions after control iontophoresis were diminished as compared to histamine iontophoresis in all groups: in controls, URT, PSO and AE1 ($p > 0.8$), in AE2 ($p > 0.1$).

Histamine iontophoresis

Healthy individuals serving as controls showed a rapid increase of itch sensation after iontophoresis, followed by a slow decrease (Fig. 1). The maximum itch ratings from patients with PSO or URT were reached later; no significant differences in these patients as compared to controls were found over the course of time. In contrast, atopic patients (AE1, AE2) reported weaker itch sensations after histamine. Time plots of the atopics showed only a slow increase in itching, with no significant differences as compared to itch ratings after control stimulus (methylcellulose).

Flare reactions

In all individuals flare reactions were measured. No differences were found between controls and atopic volunteers who were devoid of acute eczema (AE1). In contrast to these, significantly smaller flare areas were measured in patients with PSO and URT.

AE patients with acute skin symptoms (AE2) reacted with significantly diminished flare areas compared to all groups (Fig. 2).

DISCUSSION

In this study we used the established and validated method (1, 8, 10) of iontophoresis of histamine application and could demonstrate, as in former investigations (1, 8), diminished histamine-induced itch and vasoreactions in patients with AE, whereas in patients with URT and PSO only flare areas were reduced while itch intensity was similar to that of healthy controls. Symptom-free atopic individuals (AE1), reacting with "normal" axon-reflex erythema, however, reported a significantly weaker itch sensation compared to PSO, URT and controls.

Flare reactions to histamine are mediated by an axon-reflex type reaction of afferent C-fibers (11) and therefore, in all volunteers with acute skin disease (URT, PSO and AE2) this function of unmyelinated afferent cutaneous nerve fibers seems to be impaired.

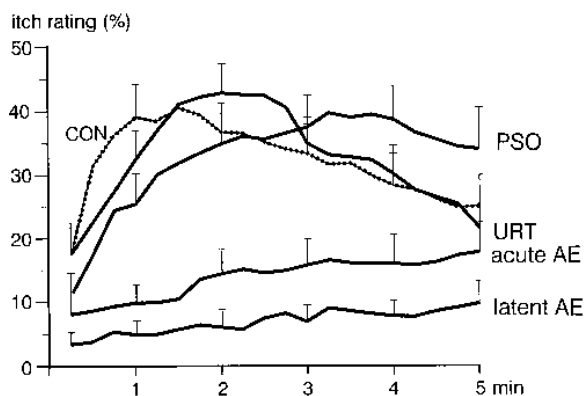


Fig. 1. Time courses of itch rating after finishing histamine iontophoresis. (Mean \pm SEM); CON=healthy controls, PSO=patients with psoriasis, URT=patients with urticaria, AE=patients with atopic eczema.

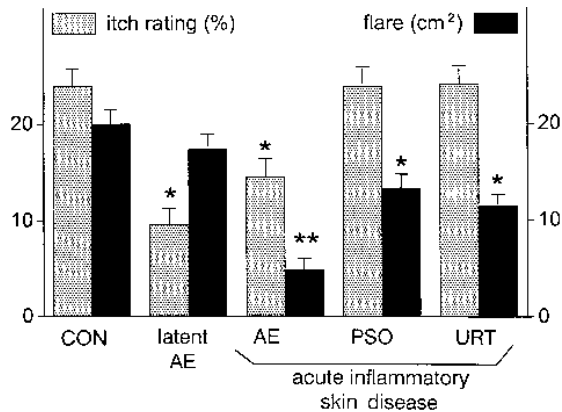


Fig. 2. Itch rating (square root of AUC) and flare size (cm²) in the five groups (mean \pm SEM). Itch ratings of latent atopic eczema (AE) and acute AE (*) are significantly different from all other groups. Flare reactions of psoriasis (PSO) and urticaria (URT) (*, $p < 0.05$) differed significantly from controls (CON) and latent AE; flare reactions of acute AE (**, $p < 0.01$) differed significantly from all other groups.

As discussed in former studies of AE patients (1, 2, 8), elevated levels of inflammatory mediators in the perireceptor milieu might result in a downregulation of histamine acting at the respective receptors, causing a weaker vasodilation after additional histamine stimulus compared to healthy subjects or symptom-free atopics. Furthermore, an increased degradation of histamine by e.g. the enzyme diamine oxidase can be discussed but has not been proved.

Although we always chose unaffected skin as the test area, we cannot exclude that the diminished flare reactions in the "acute" patient groups express tachyphylaxis to histamine due to actual mast cell-released histamine and other mediators, caused by minor, invisible urticarial or eczematous reactions present at the test area, since we did not take biopsies from the skin sites.

Otherwise, special care was taken to ensure that no influencing drugs were taken prior to the experiment (see exclusion criteria under Methods).

Another explanation for the smaller flares observed in PSO and URT is a reduced release of neuropeptides which evoke vasodilation and further release of histamine from mast cells from the free endings of unmyelinated nerve fibers. On the other hand, it is also possible that these "normally" released neuropeptides evoke only a reduced reaction on mast cells and vessels in acute patients. The reduced reaction might be caused by a downregulation of the responsible receptors on the target structures in accordance with the known elevated levels of neuropeptides in skin of PSO (12–14). Ongoing studies using the microdialysis technique enable the measurement of inflammatory mediators (e.g. tryptase, histamine) and will elucidate possible divergencies in levels of substances in the perireceptor environment of the different itching skin diseases. Our results of smaller flares in URT as compared to controls are in agreement with Juhlin's & Pihl-Lundin's findings (15). They mention a tachyphylaxis to histamine, which is quite probable since histamine seems to be the main mediator in URT. Furthermore, a disorder in the histamine metabolism could also contribute to the situation described above.

Capsaicin, known to induce release of neuropeptides from unmyelinated nerve fiber endings, induced smaller flares in PSO, reflecting a disturbance in the development of neurogenic inflammation, which affirms our results (16).

The unimpaired intensity of itch sensation in patients with URT and PSO indicates that unmyelinated C-fibers, responsible for mediating pruritus to the central nervous system, seem to be unaffected in their afferent sensory nervous function. Therefore, the alteration or disturbance in the histamine reaction in URT and PSO, reflected in a weaker neurogenic inflammation, seems to be located in the periphery, whereas the central nervous mechanisms resulting in the feeling of the sensation are unimpaired.

An increase of substance P-containing epidermal nerve fibers in psoriatic lesions was found by Naukkarinen et al. (12), who considered an important pathophysiological role for substance P in PSO. Elevated levels of vasoactive intestinal peptide in contrast to decreased substance P content in psoriatic plaques but not in uninvolved skin are described by Pincelli et al. (17). That local neurogenic inflammation causes the erythema in PSO is supposed by Krogstad et al. (18).

In accordance with our former studies (8), both AE patients suffering from acute skin disease and those being symptom-free at the time of the study reacted with a significantly weaker itch sensation after histamine.

In contrast to PSO and URT patients, who reacted with significantly smaller flares but with similarly intense histamine-induced itch sensations as compared to the controls, symptom-free AE patients (AE1) experienced significantly weaker itching but undiminished flare areas. As previously discussed, a "normal" flare reaction indicates unimpaired responsiveness of itch-mediating nerve fibers, and the attenuation of itch ratings in parallel to undiminished flares may point to a central nervous origin of the lowered itch responsiveness to histamine in volunteers with a history of AE. This finding is in agreement with those of our previously reported study (19), in which histamine evoked weaker pruritogenic reactions in AE patients: diminished itch sensation and smaller areas of alopecia or total lack of mechanically induced alopecia (= itchy skin).

In conclusion: the impaired neurogenic inflammation, seen as smaller axon-reflex erythema in all the investigated patients with acute skin diseases (AE2, PSO and URT), can be explained by a downregulation of histamine or neuropeptide receptors on the different target structures. A disorder in the release and metabolism of these mediators has to be considered as well. The cause of the weaker histamine-induced itch responsiveness in both groups of AE is assumed to be located within the central nervous system.

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