

Dermal and bronchial hyperreactivity in urticarial dermographism and urticaria factitia

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For investigation of a possible relationship between cutaneous and bronchial hyperreactivity, 74 subjects were grouped according to the presence ($n=33$) or absence ($n=41$) of urticarial dermographism after application of a standardized shearing pressure with a dermographometer (12.7×10^5 Pa). The two groups did not differ in age, sex, smoking habits, presence of urticaria and atopy, or serum IgE levels. Erythema of the dermographic test sites was always significantly greater ($P<0.001$) in the group with urticarial dermographism at 2, 4, and 8 min, and cutaneous reactivity with titrated prick tests was significantly increased in this group with low concentrations of histamine, 0.01% and substance P (0.25 mM) ($P<0.05$). After bronchial provocation with acetylcholine, 51 of the 74 subjects, 25 with and 26 without urticarial dermographism, exhibited bronchial hyperreactivity. However, significantly more subjects with urticarial dermographism had an increase in airway resistance and a decrease in specific airway conductance ($P<0.05$). In the subgroup ($n=9$) of subjects with symptomatic urticarial dermographism (urticaria factitia), these differences were even more significant ($P<0.001$). These subjects also had larger skin test reactions and significantly higher IgE levels ($P<0.01$). Thus, the present data show an association, which may be based on common mechanisms of allergic inflammation, between cutaneous and bronchial hyperreactivity.

B. M. Henz, S. Jeep, F. S. Ziegert, J. Niemann, G. Kunkel

Department of Dermatology and Asthma Poliklinik, Virchow Klinikum, Humboldt Universität zu Berlin, Berlin, Germany

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Prof. Dr B. M. Henz
Hautklinik
Virchow Klinikum
Augustenburgerplatz 1
13353 Berlin
Germany

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While the skin almost invariably reacts with redness to shearing forces, an excessive response to such stimuli, including tissue edema, is observed in 4–50% of the normal population, depending on the force applied, and is termed “urticarial dermographism” (UD) (1–5). Similarly, 10–13% of normal adults have a hyperreactive bronchial system, with a much higher incidence in patients with chronic bronchitis (6, 7). The mechanisms underlying these reactions are poorly understood, as is the possible relationship between the hyperreactivity of the cutaneous and bronchial systems. In the present investigation, we set out to study the latter question in a larger group of subjects including urticaria patients, since the latter have been reported not to exhibit increased UD (1, 2). We have carefully evaluated the medical history of all subjects regarding smoking habits and atopy; have studied the cutaneous response to physical stimuli, various pharmacologic

agents, and allergens; and have performed pulmonary function tests before and after bronchial provocation with acetylcholine (ACh). Subjects exhibiting symptomatic dermographism or urticaria factitia (UF), defined as pruritus in association with UD (8), were also analyzed separately. The data do indeed show an association between cutaneous reactivity and specific parameters of bronchial hyperreactivity.

Material and methods

Overall, 74 test subjects were recruited for the study and gave informed consent. They were at least 18 years old and had not taken corticosteroids, disodium cromoglycate, or antihistamines by any route for at least 5 days (astemizole 4 weeks). Patients and subjects with a history of mastocytosis, bronchial asthma, or chronic bronchitis were

excluded. Of the 21 patients recruited from the department, 15 suffered from chronic and three from acute urticaria, and three had allergic rhinitis. The remaining subjects were volunteers recruited from clinic personnel and medical students.

All subjects were questioned about smoking habits, routine drug use, and family and personal history of atopic disease, chronic bronchitis, and UD.

Dermographism tests were done with a dermatographometer (kindly donated by Hoffmann La Roche, Mijdrecht, The Netherlands). The rounded distal end of the metal pin had an area of 3.1 mm² and was pushed through its protective sheath by a spring-loaded device, yielding a pressure of 400 g. The pen was drawn over the test area on the right and left upper back through a template which was 10 cm long. The pressure thus applied to the skin was 12.7×10^5 Pa.

After 2, 4, and 8 min, the outer borders of wheal and erythema at the test sites were marked with a pen. After 8 min, all pen markings were transferred to transparent adhesive tape, and the mean values of redness and whealing were calculated from the measurements of each subject. When whealing had been recorded at any time point, the subject was classified as having UD. Subjects were also asked throughout the testing whether they experienced itching at the test sites; if this occurred at any time, symptomatic dermatographism (or urticaria factitia [UF]) was diagnosed.

In order to evaluate the presence of atopy, prick tests were done on the forearm of all subjects with a lancet and the following allergens: allergen mixes for tree pollen (I and II), grass, herbs, and *Dermatophagoides pteronyssinus* and *D. farinae*, as well as dog, horse, and cat allergens (Allergopharma, Reinbeck, Germany). Reactions were evaluated as described before (9). Subjects were classified as atopic when at least one skin test was positive.

Titred prick tests were also done in duplicate on the lower forearm with histamine (Allergopharma), dissolved in normal saline at 1%, 0.1% and 0.01% ACh (Dispersa, Germering, Germany); is in normal saline at 40%, 20%, and 10%; and substance P (Serva, Heidelberg, Germany) in PBS at 1, 0.5, and 0.25 mM concentrations. Readings were done at 12 min by marking the outer border of wheal and erythema at four points at a 90° angle with a pen and transferring the values to transparent tape. Mean values were calculated for each reaction from the four values obtained from the diameter of each duplicate reaction.

Pulmonary function tests were done with a body plethysmograph (Erich Jaeger, Würzburg, Germany). After a basal reading, subjects inhaled

a nebulized 1% ACh solution, and readings were done at 2 and 5 min. In case of bronchial hyperreactivity, 400 mg of salbutamol was given by inhalation to test the reversibility of the reaction. Bronchial hyperreactivity was defined as the following changes after ACh inhalation, according to Engström (10):

- 1) increase of *R*_{aw} (resistance of airways) of at least 50%
- 2) decrease of *sGaw* (specific conductance of airways) by at least 35%, and/or
- 3) decrease of FEV₁ (forced expiratory volume in 1 s) by at least 20%.

Seventy-one subjects consented to have blood taken to measure total serum IgE, IgA, IgG, IgM, and α_1 -antitrypsin levels.

Statistical analyses were done by standard methods, as detailed in the Results section.

Results

Of all subjects tested, 33 (44.6%) reacted with UD in the dermatographometer test, and nine (27.3%) of them experienced simultaneous itching and were thus classified as having UF. As shown in Table 1, subjects with and without UD did not differ in age, sex, and previous history of urticaria or atopy. More patients with concurrent urticaria had dermatographism, were aware of their cutaneous reactivity, and had slightly more positive prick tests to at least one allergen. Six of the 15 subjects with positive prick tests and UD reacted to several allergens, as did nine of 12 subjects in the group without UD. There was no statistically significant correlation between atopy and simple UD ($\chi^2 = 1.82$).

All 74 subjects reacted with erythema when tested for dermatographism. The size of the erythematous reactions on stroking was always significantly larger in patients with UD at all time points measured (Fig. 1). Only 26 of the 33 subjects with UD had whealing 2 min after stroking, and 32 after 4 min, and in four subjects, whealing had already disappeared by 8 min. There was an increase in the

Table 1. Basic data, shown as numbers of subjects, unless otherwise noted

	UD	no UD
<i>n</i>	33	41
Mean age (years)	32.6 ± 11.9	31.4 ± 11.3
M/F	17/16	20/21
Smoking	15	16
Urticaria, concurrent	12	7
Urticaria, previous	3	4
Known UD	14	1
Atopy, patient	16	23
Atopy, family history	3	3
Positive prick test, allergens	15	12
Bronchial hyperreactivity	25	26
Serum IgE, U/ml	215.55 ± 315.09	135.08 ± 214.32

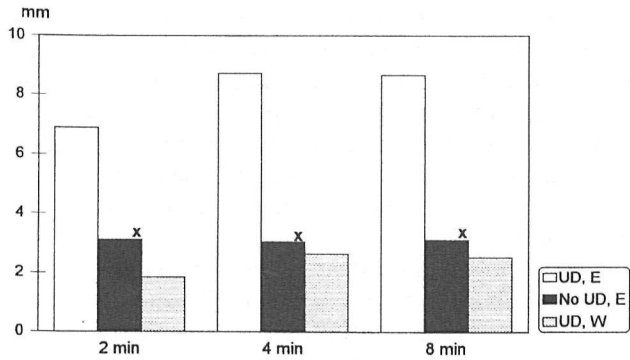


Fig. 1. Mean diameter of wheal (W) and erythema (E) in subjects with and without UD at different time intervals after elicitation with dermatographometer. * $P < 0.001$, comparing E in groups with and without UD (first two columns).

size of erythema and whealing in UD patients 2–4 min after stroking, with a slight decrease already after 8 min, whereas the erythema of patients without UD remained approximately the same over the 8 min of measurement (Fig. 1).

On prick testing, the size of wheals and erythematous reactions increased in both groups with

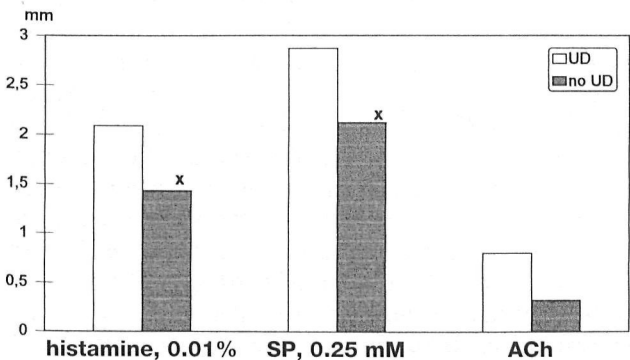


Fig. 2. Mean diameter of wheals in subjects with and without UD after prick tests with histamine, substance P (SP), and acetylcholine (ACh) at concentrations shown. * $P < 0.05$.

increasing concentrations of histamine. The same held for wheals after substance P and for wheal and erythema reactions after ACh injections (not shown). Erythematous reactions to substance P had already disappeared in all cases at the 12-min reading time, and whealing in reaction to ACh was observed in only a small number (up to 12) of subjects at any of the concentrations tested. The size of all reactions of patients with UD was always greater after injections with histamine, substance P, and ACh, but differences between the groups with and without UD were most pronounced with the lowest concentrations of test substance, and statistical significance according to the Mann-Whitney test was reached only for the lowest concentrations of histamine and substance P (Fig. 2).

On separate analysis of patients with UF, the mean values for erythema and whealing after stroking were always higher than for UD subjects without UF (Table 2), although differences did not reach statistical significance. The same held for reactions to histamine, substance P, and ACh injections (Table 2). However, significance (Mann-Whitney U-test, $P < 0.05$) was reached when the lowest concentrations of histamine and substance P were compared between nonsymptomatic UD subjects and subjects without UD (not shown). There were no marked clinical differences between the two groups (Table 2), and no statistically significant differences in presence of atopy ($\chi^2 = 0.78$).

During pulmonary function tests, 51 of the 74 test subjects (68.9%) exhibited bronchial hyperreactivity after ACh provocation. Airway obstruction in these persons was always reversible after inhalation of salbutamol. The incidence of bronchial hyperreactivity in the two groups was about equal (Table 1). However, a comparison of individual pulmonary function tests yielded significant differences (Mann-Whitney U-test) in the Raw increase

Table 2. Mean $\pm$ SD of whealing (W) and erythema (E) in patients with symptomatic dermatographism (urticaria factitia=UF) on stroking or after injection of several test substances

Skin test		UF (n=9)*	UD, no UF (n=24)**
Dermatographism	E, 2 min	13.25 $\pm$ 9.20	10.55 $\pm$ 8.00
	E, 4 min	11.39 $\pm$ 9.84	7.73 $\pm$ 6.49
	E, 8 min	12.25 $\pm$ 9.46	7.72 $\pm$ 5.88
	W, 2 min	1.89 $\pm$ 1.17	1.81 $\pm$ 1.00
	W, 4 min	3.05 $\pm$ 1.82	2.47 $\pm$ 0.60
	W, 8 min	2.74 $\pm$ 2.22	2.42 $\pm$ 0.90
Histamine, 0.01%	E	2.89 $\pm$ 4.58	4.99 $\pm$ 7.18
	W	2.13 $\pm$ 1.34	2.07 $\pm$ 1.57
Substance P, 0.25 mM	W	2.69 $\pm$ 1.47	2.81 $\pm$ 1.18
	E	8.81 $\pm$ 6.77	6.62 $\pm$ 5.94
ACh, 10%	W	1.03 $\pm$ 1.47	0.80 $\pm$ 1.44
	E		

* Four patients had chronic urticaria, four had at least one positive prick test, and one each had history of allergic rhinitis and asthma.

** Eight patients had chronic and two acute urticaria, 11 had at least one positive prick test, six had history of allergic rhinitis (including one with atopic dermatitis), and one had history of allergic asthma.

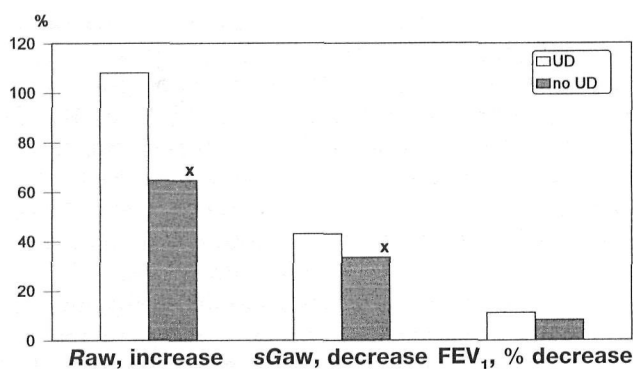


Fig. 3. Mean values of pulmonary function tests in subjects with and without UD. * $P < 0.05$.

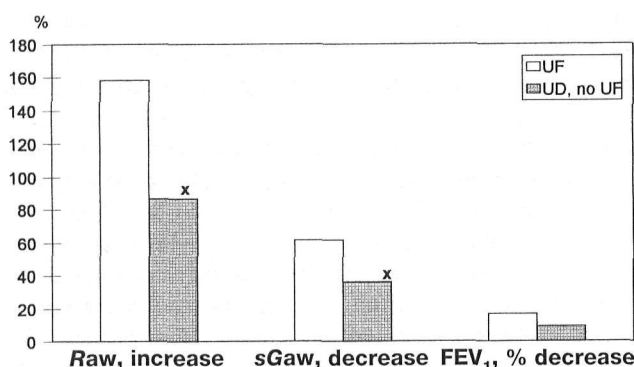


Fig. 4. Mean values of pulmonary function tests in subjects with UF and with UD without pruritus. * $P < 0.001$.

and the *sGaw* decrease, but not the FEV₁ decrease, after ACh provocation (Fig. 3).

On separate analysis of the nine subjects with UF, all were found to have a hyperreactive bronchial system on ACh provocation. Statistical analysis with the chi-square test showed a significant difference between UF patients, compared to subjects without UD ($\chi^2=4.7$), but not compared to the remaining patients with UD ($\chi^2=0.07$). Differences between subjects with UF and without UD were also highly significant in the *Raw* increase and the *sGaw* decrease, but not in the FEV₁ decrease (Fig. 4).

Mean serum IgE levels were higher, comparing subjects with and without UD (Table 1), but statistical significance was reached only when the levels of patients with UF (357.22 ± 308.40 IU/ml) were compared to those without UD ($P < 0.01$; Mann-Whitney U-test). No significant differences were noted for any of the other serum values tested (not shown).

Discussion

The present study provides the first evidence of a relationship between cutaneous and bronchial hyperreactivity in normal young adults. The data

were even more striking when subjects with more intense, pruritic cutaneous reactions (UF) were analyzed. Furthermore, they concur with previously published data on cutaneous and bronchial hyperreactivity in patients with cholinergic urticaria (11), although this association does not hold for other types of urticaria such as common acute and chronic urticaria (1–3).

The population studied here is unusual because of the relatively high incidence of UD and bronchial hyperreactivity. This may be due to the vigorous test conditions employed during dermatographism testing, since a similarly high incidence of UD was observed previously only with pressures above 9.4×10^5 Pa (1, 5). The high incidence of bronchial hyperreactivity may be explained by the high overall incidence of atopy in the study population, which, however, approximates that observed recently in a normal Berlin student population (36.4%) (12). Nevertheless, the higher incidence of individual parameters of bronchial hyperreactivity among subjects with UD cannot be explained by an increase of predisposing factors such as smoking and atopy because these were evenly distributed among the groups with and without UD (Table 1).

Although there was a wide scatter in the cutaneous reactivity of different subjects in the dermatographometer test, there were clear, statistically significant differences in the size of the erythema between the groups with and without UD and again among those with UF in the latter group (Table 2, Fig. 1). The reflex erythema surrounding urticarial wheals is currently thought to be mediated by an axon reflex and by release of substance P from free nerve endings in the skin (13, 14).

Similar mechanisms are thought to operate in asthmatic reactions (15). Substance P is of special interest in immediate allergic reactions since it also causes bronchial edema and bronchoconstriction and since it can induce mediator release from mast cells and vagal nerve endings (reviewed by Maggi [16]). Increased cutaneous reactivity to substance P has been reported in patients with asthma, compared to controls (17), and the neutral endopeptidase which degrades substance P is elevated in the serum of asthmatics, with a positive correlation to bronchial hyperreactivity (18). In the skin, increased levels of substance P have also been demonstrated in urticarial lesions (19), and subjects with UD exhibited enhanced whealing reactions in response to this mediator (Fig. 2). The fact that statistical significance was reached only at the lowest test concentrations of substance P, as held also for histamine, may be due to subtle pharmacologic changes in the target tissue, e.g., in receptor levels or cellular responsiveness, which could be dealt with in prick tests with higher test doses. The same holds

for bronchial hyperresponsiveness, as defined in the literature (10), where overall hyperreactivity is not different in subjects with or without UD, but statistically significant differences were noted in individual pulmonary function parameters after ACh provocation, particularly in UF (Figs. 3 and 4).

While the mechanisms involved in ordinary UD are poorly understood, the data for UF are particularly interesting since in this disorder, IgE antibodies have been shown to play a role (20). All our UF subjects also had significantly elevated serum IgE levels. It is thus conceivable that mast cells are activated subclinically in this disorder, with an associated mediator release that would induce various changes in receptor expression and responsiveness of resident bronchial and cutaneous tissue and infiltrating inflammatory cells (reviewed by Weber et al. [21]). We have seen a marked upregulation of integrins and endothelial adhesion molecules in various types of urticaria, and partly also in clinically uninvolved skin (22, 23). Bronchial tissue would probably be similarly affected, thus explaining the bronchial hyperreactivity in all UF subjects in this study.

References

- Breathnach SM, Allen R, Ward AM, Greaves MW. Symptomatic dermographism: natural history, clinical features, laboratory investigations and response to therapy. *Clin Exp Dermatol* 1983;8:463-76.
- Fisher AA, Schwartz S. Low incidence of dermographism in subacute and chronic urticaria. *Arch Dermatol Syphilol* 1953;68:553-5.
- Grolnick M. An investigative and clinical evaluation of dermographism. *Ann Allergy* 1970;28:395-404.
- Kirby JD, Matthews CNA, James J, Duncan EHL, Warin RP. The incidence and other aspects of factitious wealing. *Br J Dermatol* 1971;85:331-5.
- Wong RC, Failrey JA, Ellis CN. Dermographism: a review. *J Am Acad Dermatol* 1984;11:643-52.
- Britton J, Pavord I, Richards K, et al. Factors influencing the occurrence of airway hyperreactivity in the general population: the importance of atopy and airway calibre. *Eur Respir J* 1994;7:881-7.
- Woolcock AJ, Peat JK, Salome CM, et al. Prevalence of bronchial hyperresponsiveness and asthma in a rural population. *Thorax* 1987;42:361-8.
- Jeep S, Czarnetzki BM. Urtikarieller Dermographismus, Urticaria factitia, Druckurticaria. *Allergologie* 1994;17:12-16.
- Wagenpfeil S, Grabbe J, Jeep S, Czarnetzki BM. Reproducibility of skin prick test reactions to common allergens in patients with atopic eczema. *J Allergy Clin Immunol* 1992;89:143-4.
- Engström I. The bronchial provocation test and criteria for positive reaction. *Allergy* 1980;35:256-8.
- Czarnetzki BM, Galinski C, Meister R. Cutaneous and pulmonary reactivity in cholinergic urticaria. *Br J Dermatol* 1984;110:587-91.
- Zuberbier T, Althaus C, Chantraine-Hess S, Czarnetzki BM. Prevalence of cholinergic urticaria in young adults. *J Am Acad Dermatol* 1994;31:978-81.
- Barnes PJ, Brown MJ, Dollery CT, Fuller RW, Heavey DJ, Ind PW. Histamine is released from skin by substance P but does not act as the final vasodilator in the axon reflex. *Br J Pharmacol* 1986;88:741-5.
- Foreman JC, Jordan CC, Oehme P, Renner H. Structure-activity relationships for some substance P-related peptides that cause wheal and flare reactions in human skin. *J Physiol* 1983;335:449-65.
- Barnes PJ. Asthma as an axon reflex. *Lancet* 1986;1:242-5.
- Maggi CA. Tachikinin receptors and airway pathophysiology. *Eur Respir J* 1993;6:735-42.
- Iwamoto I, Kimura A, Tanaka M, Tomioka H, Yoshida S. Skin reactivity to substance P, not neurokinin A, is increased in allergic asthmatics. *Int Arch Allergy Appl Immunol* 1990;93:120-5.
- Niehus J, Ratti H, Zhang M, Lucas C, Kunkel G. Correlation between neutral endopeptidase (NEP 3.4.24.11) in serum and bronchial reactivity to acetylcholine. *J Pharm Ther* 1994;3:59-64.
- Wallengren J, Möller H, Ekman R. Occurrence of substance P, VIP and CGRP in dermographism and cold urticaria. *Arch Dermatol Res* 1987;279:512-15.
- Newcomb RW, Nelson H. Dermographia mediated by immunoglobulin E. *Am J Med* 1973;54:174-80.
- Weber S, Krüger-Krasagakes S, Grabbe J, Zuberbier T, Czarnetzki BM. Mast cells. *Int J Dermatol* 1995;34:1-10.
- Haas N, Iwen W, Hamann K, Grabbe J, Figdor C, Czarnetzki BM. b2-Integrins in different forms of urticaria. *Br J Dermatol* 1995;133:48-53.
- Haas N, Wesendahl C, Czarnetzki BM. Endothelial adhesion molecules in immediate and delayed urticarial whealing reactions. *Arch Dermatol Res* 1994;286:169.

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