Aromatic components of food as novel eliciting factors of pseudoallergic reactions in chronic urticaria

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Background: Pseudoallergic reactions (PARs) against both additives and natural foods have been reported to elicit chronic urticaria, but in natural food the responsible ingredients are largely unknown.
Objective: The study was aimed at identifying novel pseudoallergens in food and focused on evaluating tomatoes, white wine, and herbs as frequently reported food items eliciting wheal responses in urticaria.
Methods: In 33 patients with chronic urticaria and PARs to food (proved by means of elimination diet and subsequent re-exposure with provocation meals), oral provocation tests were performed with field-grown tomatoes, organically grown white wine (whole food, steam distillates, and residues), oily extracts from herbs, and food additives. In addition, skin biopsy specimens from patients were studied for in vitro mast-cell histamine release with tomato distillate alone or on subsequent stimulation with anti-IgE, substance P, and C5a.
Results: Seventy-six percent of patients reacted to whole tomato (steam distillate, 45%; residue, 15%), 50% to food additives, 47% to herbs, and 44% to whole wine (extract, 27%; residue, 0%). Histamine, protein, and high levels of salicylate were only found in residues. The tomato distillate was further analyzed by means of mass spectroscopy, identifying low-molecular-weight aldehydes, ketones, and alcohol as major ingredients. In vitro histamine release was not caused by tomato extract itself but was enhanced by means of subsequent stimulation with substance P and C5a but not by anti-IgE.
Conclusion: Aromatic volatile ingredients in food are novel agents eliciting PARs in chronic urticaria. Histamine, salicylate, and a direct mast-cell histamine release are not involved in this reactivity to naturally occurring pseudoallergens. (J Allergy Clin Immunol 2002;109:343-8.)

Key words: *Food intolerance, tomato, wine, herbs, histamine release, skin mast cells*

Abbreviation used
PAR: Pseudoallergic reaction

Chronic urticaria, defined as spontaneously evolving wheal responses that last for at least 6 weeks, can be induced by a wide variety of agents, including allergens or pseudoallergens in food and drugs, infectious agents, and autoantibodies.[1]

Although IgE-dependent mediator release from mast cells is of little importance in chronic urticaria, pseudoallergic reactions (PARs) have frequently been discussed as playing a major role.[2,3] PARs are associated with histamine release from cutaneous mast cells, and at least in aspirin-dependent reactions, leukotrienes also seem to play a major role.[4] Diagnosis is difficult because pseudoallergy can only be proved with oral provocation tests. Skin test responses are negative, and specific IgE antibodies play no pathogenetic role.[5]

Pseudoallergic urticarial reactions have been shown to be elicited by a broad range of agents, including nonsteroidal anti-inflammatory drugs like aspirin and natural or added food ingredients like salicylates, benzoates, and tartrazine.[2,6,7]

In a group of unselected patients with chronic continuous urticaria, we observed an improvement on a diet low in pseudoallergens in 73% of patients, as proved by reduction of symptoms or remission on an elimination diet and a subsequent worsening on provocation with pseudoallergen-rich food.[8] These results were recently confirmed by Pigatto and Valsecchi,[9] who investigated 202 patients with chronic urticaria using the same diet as in our study. These authors reported that 126 patients improved on the diet, 35 patients failed to show any benefit, and 41 patients dropped out of the study. However, in double-blind, placebo-controlled challenge tests only 37% of patients improving on the diet reacted to food additives.

Taken together, these data suggest that additional as-yet-unidentified factors in food might be involved in the pathogenesis of PARs in some of the patients. The present study was therefore designed to search for naturally occurring pseudoallergens in food. Investigations were focused on sun-ripened tomatoes, white wine, and herbs as the most frequently suspected food items and also on

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TABLE I. Pseudoallergens used for provocation tests (in gelatin capsules)

Pseudoallergens	Name	E-number	Dose
Coloring agents			
Azo-dyes	Tartrazine	E102	50 mg
	Sunset yellow	E110	5 mg
	Azorubine	E122	5 mg
	Amarante	E123	5 mg
	Ponceau	E124	5 mg
	Brilliant black BN	E151	5 mg
Other synthetic dyes	Quinolone yellow	E104	5 mg
	Erythrosine	E127	5 mg
	Patent blue	E131	5 mg
	Indigotine	E132	5 mg
Natural colors	Iron (III) oxide	E172	5 mg
	Red cochineal	E120	5 mg
Preservatives	Sorbic acid	E200	1000 mg
	Sodium benzoate	E211	1000 mg
	p-Hydroxy benzoate	E214-219	1000 mg
	Sodium metabisulfite	E223	50 mg
	Sodium nitrate	E251	100 mg
Antioxidants	Butylhydroxyanisol (BHA)	E320	50 mg
	Butylhydroxytoluol (BHT)	E321	50 mg
	Propylgallate	E310	50 mg
	Tocopherol	E306-309	50 mg
Taste enhancer	Monosodium glutamate	E621	200 mg
Naturally occurring substances	Salicylic acid		100 mg

the patients' history. Efforts were made to identify individual ingredients in these foods that might be responsible for the urticarial reactions, and finally, their possible effect on histamine release from skin mast cells was investigated. The data obtained strongly suggest that natural aromas in food represent newly discovered pseudoallergens and eliciting stimuli in chronic urticaria.

METHODS

Subjects

A total of 33 patients (22 female and 11 male patients; mean age, 47.8 years; range, 16-70 years) with chronic urticaria and daily spontaneous occurrence of wheal responses was recruited for the study. All had previously experienced symptom improvement on a pseudoallergen-free diet, as detailed previously,[1,8] and symptoms had recurred on exposure to a full, pseudoallergen-rich meal. Five patients also had physical urticaria (2 cholinergic, 2 dermographic, and 1 heat); 3 had additional skin test–proved type I allergy to birch, mite, and peach allergens, respectively, as proved by appropriate provocation tests[5]; 2 had thyroiditis; and 1 each was given a diagnosis of *Helicobacter pylori*–associated gastritis and aspirin intolerance. Type I allergy against the food items used in the provocation tests was excluded with skin tests with the native food (prick-to-prick test). In addition, specific IgE (Pharmacia CAP) results for tomato were negative in all patients.

All subjects had given written consent to participate in the study.

Preparation of food extracts

One large batch each of field-grown, sun-ripened Canary Island tomatoes; greenhouse tomatoes (for mass spectroscopy only); and organically grown dry white wine from France was purchased for the study.

Aliquots of 100 g of tomatoes were blended and immediately put into boiling water for 10 seconds for inactivation of enzymes. The latter step was omitted for wine. Separation into volatile compounds and residues was performed by means of Antonacopulos steam distillation for 2 to 3 hours because extraction with organic solvents was unsuitable for subsequent oral provocation tests or in vitro studies. Steam distillation furthermore allowed the extraction of substances with boiling points higher than that of water. Only the first 100 mL of each steam extract containing the volatile components of tomatoes or wine were collected.

In addition, extracts (oils) from the following herbs were purchased: basil, fenugreek, cumin, dill, ginger, coriander, caraway, curcuma, parsley, pepper, rosemary, and thyme (Rothe, Germany). Mixed extracts were placed in capsules in an amount equaling the average intake of these herbs in well-seasoned food.

Analytic procedures

Extracts, residues, or both were further analyzed for contents of salicylic acid by means of UV-VIS spectrophotometry at 237 nm, for histamine by using a commercially available enzyme immunoassay (Dianova, Hamburg, Germany), and for SO_2 in wine by using a sequence of distillations, followed by measurements of iodine, according to the method of Diemair et al.[10]

For gas chromatographic and mass spectrometric investigation of the volatile agents in the tomato steam distillates, at least 1 kg of tomatoes was extracted, as described above. The combined steam distillates were then extracted with diethylether and dried with sodium sulfate, and the organic fraction was concentrated to 50 µL under mild conditions on a vigreux column. n-Heptane was added as an internal standard. One microliter of the concentrate was injected together with a mixture of aliphatic hydrocarbons (chain length C-7 to C-20) for determination of the relative retention indices of the volatile compounds by using a gas chromatograph 9610 (Split-Splitless Injector [Finnigan, Germany] connected with a Finnigan MAT 4510 Quadrupole mass spectrometer) at an injection temperature of 250°C with a fused silica capillary column (DB1; 60 × 0.32 mm intradermally, 1 µm film thickness) and helium (30 cm/s, 35°C) as the carrier gas. The following additional conditions were used: split,

1:5; initial temperature, 35°C; initial time, 5 minutes; temperature rate, 2°C/min; and end temperature, 280°C. Relative quantification of the main compounds was performed by calculation of their respective peak areas in relation to the n-Heptane internal standard peak area. The mass spectra of interest were electronically compared with proposed electronic spectra derived from the National Buero of Standardization database. The main compounds were identified by means of comparison of their mass spectra with respective spectra and relative retention indices from authentic reference substances.

Oral provocation tests

All patients were orally challenged on consecutive days with 200 g of Canary Island tomatoes, 200 mL of French white wine, and a mixture of herbal extracts (oils). Because of the large amounts of test material, provocation tests with wine and tomato could not be blinded. In case of positive reactions against tomato or wine, further challenge tests were performed with equivalent amounts of extracts and residues as with native food (see above) and with salicylate and sodium metabisulfite. In addition, double-blind provocations were performed with a mixture of conventional pseudoallergens in food at the concentrations listed (Table I).[5] The placebo consisted of the same number of capsules of the same color and size filled with silicium oxide-mannite.

Clinical reactions were assessed and rated as follows: –, negative; (+), questionable, only pruritus; +, mild, with few wheals; or ++, marked, with extensive wheals. In case of + or ++ reactions, no oral challenge tests were performed on the subsequent day to avoid false-negative responses caused by tachyphylaxis.

In vitro tests

For studies of mast-cell histamine contents and release, skin biopsy specimens were taken from consenting patients and from normal volunteers. After weighing, biopsy specimens were minced; enzymatically dispersed after a 1-hour incubation with collagenase and hyaluronidase, as previously described[11-13]; and divided into 6 equal parts. Each sample was preincubated for 30 minutes with buffer, tomato extract, or the mixture of pseudoallergens described above (diluted 1:500 in buffer to simulate the tissue concentration during oral provocation) and then challenged for another 30 minutes with anti-IgE (400 IU/mL; Behring, Marburg, Germany), C5a (10^{-7} mol/L; Sigma, Munich, Germany), substance P (30 µmol/L, Sigma), or buffer control (for spontaneous release). Histamine contents in tissue extracts lysed with 2% perchloric acid (total cellular histamine) and in supernatants were measured by means of enzyme immunoassay (see above), and release was calculated as a percentage of total histamine after subtraction of spontaneous release.

Statistics

Significance of results was calculated by using the Student *t* test.

RESULTS

Provocation tests

None of the patients studied reacted to any of the test substances on prick testing, and no specific serum IgE to tomato was found in any of the blood samples. Urticarial reactions after oral challenge occurred after a mean latency period of 2 to 4 hours. False-positive reactions on double-blind provocation with placebo were not seen.

Data on the frequency and degree of clinical reactions of the patients with urticaria to the different reagents after oral provocation are summarized in Fig 1 and Table II. The frequency of positive reactions, considering ++ and + reactions only, was highest for whole tomato (76%), with 45% of patients reacting to the distillate and 15% to the residue. Numbers were also high for patients reacting to the pseudoallergen mixture (50%), followed by reactions to herbs (47%), unfractionated wine (44%), and wine extract (27%). Only 1 (6%) patient reacted to sodium metabisulfite (but not to wine), and none reacted to the wine residue.

Of the patients with pseudoallergy against food, all but 2 reacted to at least one of the test substances. Table III shows that tomatoes were not only the most frequent cause of reactions to a single agent or food item but also that 69.8% of tomato-reactive patients were positive for at least one additional item tested. Percentages of patients reacting to white wine or pseudoallergen mixture only were much lower (7.7% and 8.3%, respectively), and only one patient showed crossreactivity with these 2 agents. The only patient who reacted to sodium metabisulfite (Table II) was also reactive to tomato and its distillate and to the pseudoallergen mixture, but he did not to react to white wine, probably because of the low levels of sulfite contained therein.

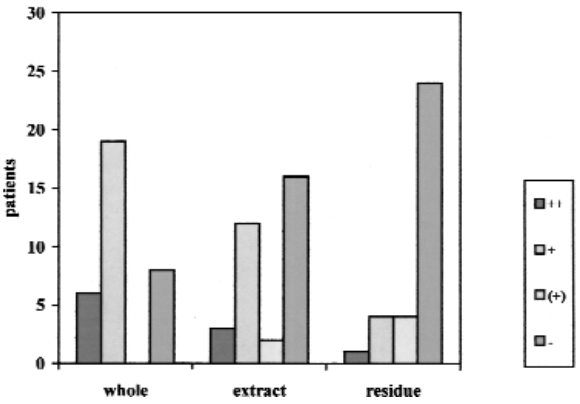

FIG 1. Clinical reactivity to tomato after oral provocation. Numbers of reacting patients are shown on the ordinate, and reactivity to whole tomato, extract, and residue are shown on the abscissa. The *columns* show the severity of reactions, with columns representing positive (++, marked, with extensive whealing; +, mild with few wheals; (+), questionable, only pruritus) and negative reactions from left to right (see also Table II).

TABLE II. Number of patients reacting to different agents on oral provocation

Test substance (No. of patients tested)	No. of patients with clinical reactivity			
	++	+	(+)	–
Wine (26)	1	6	3	16
Wine distillate (26)	0	7	0	19
Wine residue (26)	0	0	4	22
Pseudoallergen mixture (24)	1	11	2	10
Sodium metabisulfite (17)	0	1	2	14
Salicylic acid (17)	0	0	3	14
Herbs (17)	0	8	1	8

++, Marked; +, moderate; (+), questionable, only pruritus; –, no reaction.

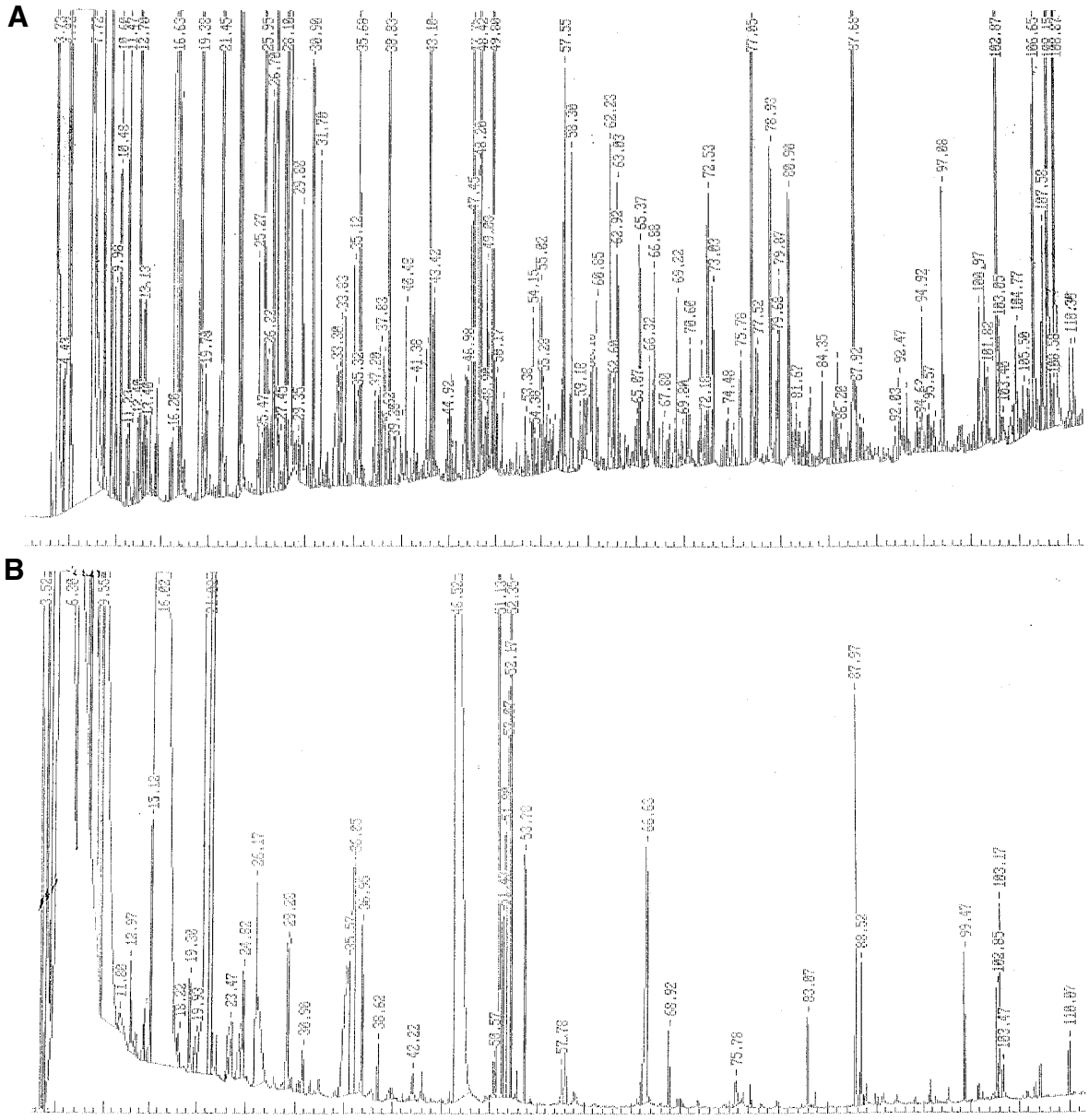

FIG 2. Gas chromatography of the tomato distillate comparing field-grown tomatoes from the Canary Islands (used in this study, **A**) and greenhouse tomatoes from The Netherlands **(B)**.

Results of analytic procedures

Because salicylic acid, histamine, or SO_2 in tomato or wine might contribute to the PARs, fractions were analyzed for their contents of these substances. As shown in Table IV, the tomato extracts contained only minor amounts of salicylic acid and no histamine, in contrast to the residue, even though reactions on oral provocation were predominantly in response to the extract (Table II and Fig 1). Furthermore, none of the patients reacted significantly to high doses of salicylic acid alone (100 mg, Table II). SO_2 levels in white wine distillate were low, and again, histamine levels were below the limit of detection, whereas values for histamine in the residue were similar to those in tomato residue.

The extract was investigated by means of gas chromatography and compared with extract from a greenhouse to identify compounds potentially arising during the ripening process and to further identify the ingredients of the tomato distillate to which the majority of the reactions were observed. By this means, more than 300 different peaks were detected in the distillate made from field-grown tomatoes, with far fewer peaks for greenhouse tomatoes (Fig 2). Further analysis of the differential display of these peaks and comparisons with data from the database, as described in the "Methods" section, showed that field-grown tomatoes contained a number of distinct ingredients, namely 5 alde-

TABLE III. Percentage of patients (n = 31) reacting to only tomato or to a combination with other foods

Reaction to:	
Tomato only	32.3
Tomato plus pseudoallergen mixture	25.0
Tomato plus white wine	15.4
Tomato plus pseudoallergen mixture plus white wine	29.4

hydes, 2 ketones, and 1 alcoholic chemical, as summarized in Table V.

Histamine contents and release from skin biopsy specimens

Skin biopsy specimens of patients and normal control subjects were closely similar in weight, whereas the total amount of histamine was significantly higher in the patients' tissue, as shown in Table VI. Furthermore, spontaneous histamine release was significantly higher from the patients' skin mast cells. As expected, tomato extract caused no increased histamine release in patient or control skin (not shown), whereas preincubation of patients' skin with tomato extract resulted in increased release on subsequent stimulation with substance P and C5a but not with anti-IgE (Table VII).

DISCUSSION

Although until now artificial food additives have been viewed as primary eliciting agents of PARs to food, the present study demonstrates that such reactions also frequently occur in response to natural ingredients in tomatoes, white wine, and herbs. The pseudoallergic nature of the reactions is demonstrated by a lack of positive skin test responses, no detectable specific serum IgE, and failure of the tomato extract to induce in vitro histamine release from patient skin mast cells.

PARs to tomatoes were the most striking finding in this study, with most reactions occurring in response to components of the steam distillate. Similarly, all reactions to wine were noted only on provocation with the distillate, and the positive reactions to herbs (Table II) are most likely also attributed to nonprotein compounds because only oils were tested. PARs are known to be dose dependent and frequently not restricted to just one agent, as underlined by the high frequency of multiple reactivities in patients with sensitivity to tomatoes (Table III). This may also explain why the numbers of clearly positive reactions on separate oral provocation to distillate and extract add up to approximately only two thirds of reactions to whole tomato. It may also account for the higher numbers of patients reacting to the pseudoallergen mixture (Table II) than expected from previous reports with oral provocation tests making use of individual preservatives and food colors.[8,14]

The data also show that salicylic acid cannot account for the reactions because no detectable levels were found in the distillate (Table IV), and none of the patients reacted to salicylate alone (Table II).

TABLE IV. Contents of known ingredients in tomato and wine that might cause or contribute to PARs

	Salicylic acid (mg/100 g)	SO_2 (mg/L)	Histamine (nmol/mL)
Tomato extract	0.68 ± 0.31	ND	0.0
Tomato residue	15.13 ± 6.79	ND	25
White wine	ND	149.0	22*

ND, Not done.
*Values in residue; extract was negative.

TABLE V. Major components in tomato steam distillate, as identified with mass spectroscopy

Compound	Molecular weight (kd)
3-Methyl butanal	86
Hexanal	100
1-Pentene-3-one	84
3-Methyl butanol	86
6-Methyl-5-heptene-2-one	127
2-(E)-Heptanal	112
2-(E)-Hexanal	98
3-(Z)-Hexene-1-al	100

Histamine was also only found in the residues of tomatoes and wine, and reactivity to this preparation was low or absent on oral provocation. This biogenic amine has been described to cause flush reactions and urticaria in patients with reduced diamine oxidase activity.[15,16] However, in the patients examined here it is unlikely to account for the reactions to the tomato residue. This concept is supported by a recent report of Kanny et al,[17] who showed that wine intolerance is independent of its histamine content. Nevertheless, we cannot rule out that some of our patients may have also had histamine sensitivity.

Sulfites have been implicated in wine-induced asthma[18] and might very well account for the reactivity to wine distillates in our patients. However, it should be noted that the values of SO_2 measured in the batch of white wine studied here are very low (Table IV) compared with the values of 150 to 400 mg/L in white or red wines measured and allowed for sale in Germany (decree of the Federal Agency, 1981). Furthermore, only one of our patients reacted to 50 mg of encapsulated metabisulfite, and this patient did not react to wine. Additional ingredients in wine must thus be responsible for PARs in patients with wine-induced asthma and urticaria. Alcohol itself might be considered because alcohol has been described to cause non–IgE-dependent urticaria and anaphylaxis in a number of patients, as also proved by elevated serum tryptase levels after double-blind challenge.[19]

Further research concentrated on tomato distillates, for which we made an attempt to identify substances possibly responsible for the clinical reactions. The large number of peaks noted on gas chromatographic analysis made this an almost impossible task. One must also consider that aromatic components in fruits and vegetables are highly variable in dependence on the composition of soil in which they are grown, the climatic conditions, and the degree of ripening, as shown in the comparison with Dutch greenhouse tomatoes (Fig 2). Although the high number of minor com-

TABLE VI. Basic data on skin biopsy specimens

Subjects (n)	Specimen weight (mg)	Total histamine contents (ng)*	Spontaneous histamine release (%)
Control subjects (5)	38.20 ± 8.14	39.65 ± 11.30	8.27 ± 1.00
Patients (14)	36.31 ± 6.08	50.55 ± 12.13†	11.00 ± 3.11‡

*Values (means ± SD) are from one sixth of the total biopsy specimen.
†$P = .012$, ‡$P = .015$ compared with normal control subjects.

TABLE VII. Percentage of histamine release from biopsy specimens of patients after preincubation with tomato extract and subsequent stimulation with anti-IgE, substance P, or C5a

	Preincubation with:	
Stimulus	Buffer (n)	Tomato extract (n)
Anti-IgE	12.36 ± 4.84 (14)	11.38 ± 4.78 (10)*
Substance P	9.75 ± 1.30 (3)	15.26 ± 5.29 (3)†
C5a	14.78 ± 3.54 (6)	17.10 ± 2.94 (6)‡

Values represent percentage of complete release minus spontaneous release (n = number of samples studied).
*Not significant.
†Statistics not calculated because of low numbers.
‡$P < .05$.

ponents cannot be ruled out to be relevant for the elicitation of PARs a priori, the dose dependency of PARs point to the relevance of the major components, which should be considered for testing in future studies. Molecules like some of the identified aldehydes (hexanals) can be generated from linoleic and linolenic acid in tomatoes by means of cleavage through lipoxygenase alone or in combination with hydroxylases. This is of interest because other pseudoallergens, particularly classical acetyl salicylic acid, are also involved in this pathway, and leukotrienes have been shown to be secreted at increased levels in aspirin-dependent asthma and in pseudoallergy to food.[19-21]

PARs are difficult to study because the mechanisms involved are not clarified, and oral provocation is the only valid method for testing. Activation of mast cells, resulting in histamine release, has been implicated in the past.[2] As expected from the increased numbers of mast cells reported even in uninvolved skin of patients with urticaria,[22] we found significantly elevated levels of total histamine and spontaneous histamine release from skin biopsy specimens in patients versus in control subjects. There was also an interesting increase in the release with the combination of tomato distillates with substance P and C5a but not on IgE receptor-dependent stimulation (Table VII), underlining the IgE-independent nature of PARs. Because of the limited accessibility of sufficient quantities of skin mast cells from patients with urticaria, only a few experiments could be performed, with only limited possibilities for statistical evaluation. These data must therefore be considered to be preliminary.

Taken together, this study implicates, by several lines of evidence, a possible novel role of volatile aromatic components in natural food in the elicitation and maintenance of chronic urticaria. The data will need to be further explored, particularly with regard to the exact nature of the different natural pseudoallergens in food and their pathogenetic role in patients with chronic continuous urticaria.

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