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Original article

Pseudoallergic reactions in chronic urticaria are associated with altered gastroduodenal permeability

Background: In a subgroup of patients with chronic urticaria (CU) the disease is caused by pseudoallergic reactions to food. The aim of this study was to investigate whether disturbances of the gastrointestinal barrier function play a role in the pathomechanism of the disease.
Methods: In 55 patients with CU gastrointestinal permeability was measured with an *in vivo* triple-sugar-test before and after 24 days of a diet low in pseudoallergens. Sucrose served as marker for gastroduodenal permeability, lactulose/mannitol ratio for intestinal permeability.
Results: Basal gastroduodenal and intestinal permeability were significantly higher in patients with urticaria as compared to controls. In 29 of the 55 patients skin symptoms decreased or completely disappeared during the diet (responders). Compared to nonresponders ($n = 26$), responders had a significantly higher gastroduodenal permeability before treatment (0.36 ± 0.04 *vs* $0.15 \pm 0.01\%$ sucrose; $P < 0.001$), which decreased after the diet (0.17 ± 0.02; $P < 0.001$). The number of patients with *Helicobacter pylori* infections did not differ between the two groups.
Conclusions: The results indicate that in a subgroup of patients with CU and pseudoallergy an impaired gastroduodenal barrier function may be of pathophysiological importance. The underlying mechanisms seem to be independent of *H. pylori* infection.

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As pointed out in a letter to the journal *Allergy* (1), we prefer the term 'pseudoallergic', especially since the eliciting agents of the nonallergic hypersensitivity reaction can be shortly called 'pseudoallergens', which corresponds to the terms 'allergy' and 'allergens', respectively.

Chronic urticaria (CU) is defined as the occurrence of spontaneous wheels for a duration of more than 6 weeks (2, 3). However, the origin is very heterogeneous. While food has been described to be of special importance in a subgroup of patients with continuous whealing also autoantibodies against the thyroid or IgE receptors (4), infections, especially *Helicobacter pylori* (5–7), other inflammatory processes and rarely true allergies have been described. While it is consensus that IgE mediated food allergy is responsible for $<1\%$ of CU cases, the frequency of patients benefiting from a diet low-in-pseudoallergens varies in the studies (Table 1). Apparently the results depend on the diet used and the study population investigated. The diet we have been describing in the past (8, 9) has been reevaluated with a similar success rate by Pigatto and Valsecchi (10). The responsible pseudoallergens include artificial food additives as well as natural food ingredients, the latter being especially low molecular weight aromatic compounds. Among the large variety of chemical substances, which have been proven, to be able to cause pseudoallergic reactions in double-blind placebo controlled challenge tests a common link regarding the possible pathomechanism is missing.

Especially in view of the existing data (8) showing that both *H. pylori* positive and negative gastritis trigger CU, disturbances of the gastric mucosa appeared to be interesting. In the present study, we have therefore investigated the permeability of gastric and intestinal mucosa with an *in vivo* triple sugar test before and after the diet low-in-pseudoallergens.

Methods

Patients

Fifty-five patients with CU of at least 3 months disease history were included in the present study ($n = 55$; 41 F, 14 M; age: 40 ± 17 years). All patients showed moderate to severe

Abbreviations: CU, chronic urticaria; PI, permeability index; NSAID, nonsteroidal anti-inflammatory drug.

Table 1. Review of studies on pseudoallergy in urticaria

Author(s)	Disease studied	Number of patients	Positive reactions to food additives	Provocation	Improvement on diet
Warin & Smith (1976) (26)	Chronic urticaria (CU)	111	59.5% (inclusive of ASS)	Single blind, placebo controlled (antihistamine treatment$)	75%*
Genton et al. (1985) (27)	CU	17	88.2% (inclusive of ASS)	Single blind	93.3%*
Michaelsson & Juhlin (1973) (28)	CU and angioedema	52	75% (inclusive of ASS)	Single blind	81.3 free of symptoms*; 6.3% improvement*
Thune & Granhold (1975) (29)	CU	100	62% (inclusive of ASS)	Single blind	80.6 improvement*; 19.4% spontaneous improvement*
Wüthrich & Fabro (1981) (30)	Urticaria	620	26.6% (inclusive of ASS)	Single blind	>60% improvement*
Juhlin (1981) (31)	CU and angioedema in 9	330	31%	Single blind	No data
Ortolani et al. (1984) (32)	CU	70	59.6% (inclusive of ASS)	Single blind, placebo controlled	No data
Rudzki (1980) (33)	CU	158	31.6%		No data
Verschave et al. (1983) (34)	CU	67	No		55% of all patients
Gibson & Clancy (1980) (35)	CU	76	Up to 54%	Single blind, placebo controlled	71.1% free of symptoms; 19.7% improvement; 9.2% refused diet of all patients
Kirchhof et al. (1982) (36)	Chronic intermittent urticaria	100	39%	Double blind, placebo controlled	44%*
Supramaniam & Warner (1986) (37)	Urticaria and angio-edema in 74,4	43	24%	Double blind, placebo controlled	87.5%*
Zuberbier et al. (1995) (8)	CU and/ or angioedema	67	19%	Double blind, placebo controlled	73% of all patients
Pigatto & Valsecchi (2000) (10)	CU	202 of 348	37.3%	Double blind, placebo controlled	62.4% improvement; 17.3% no improvement; 20.3% disrupted diet of all patients

* After positive provocation.

spontaneous occurrence of wheals almost continuously which could be easily controlled by antihistamines and no one needed corticosteroid treatment. Two patients had additional angioedema. Exclusion criteria for the present study were other forms of urticaria such as acute or chronic intermittent urticaria and physical forms of urticaria. Also patients with gastrointestinal diseases, e.g. inflammatory bowel diseases, celiac disease, and peptic ulcers, cancer, nephropathy, and those treated with drugs like corticosteroids, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and immunosuppressive agents were excluded.

On admission to the study all patients underwent a standard diagnostic procedure. Total IgE was >150 kU/l in $n = 19$ patients (CAP-test; Pharmacia diagnostics). Prick testing with common allergens was performed for screening of type I allergies in all patients. In patients suspected of suffering from an allergy to specific food, native food samples were used for prick testing as well. In none of the patients clinically relevant sensitization to food allergens was detected. Informed consent was obtained in each case for participation before the beginning of the study and antihistamine treatment was discontinued in order to evaluate skin symptoms. Patients were seen on an outpatient basis.

Twenty-seven healthy volunteers ($n = 27$; 15 F, 12 M; age: 37 ± 10 years) served as controls only for the gastrointestinal permeability tests (see below).

Diet

All patients were put on a previously evaluated strict elimination diet, low in pseudoallergens for 24 days. The diet is characterized as free from artificial food additives and containing only low quantities of known naturally occurring pseudoallergens (8, 9). Characteristic pseudoallergenic substances are for example food colourants, food preservatives, taste intensifiers, and naturally occurring substances, e.g. aromatic compounds, biogenic amines, and salicylic acid.

Evaluation of the skin symptoms

The level of urticaria was assessed by a dermatologist three times during the study period, i.e. before the onset of the diet, after 12 and 24 days. A standard severity score for wheals (number of wheals and area involved) and pruritus each ranging from $0 =$ no symptoms to $3 =$ severe symptoms based on 24 h patient history according to the guidelines was used (2, 8, 11). Since the intensity of wheals fluctuates during the day according to international consensus, the value of this score based on a patient diary has proven to be the most reliable measurement of monitoring disease activity (2) and is superior to a single time point doctor-based score. For assessment of disease activity and benefit of diet, a mean score $\pm$ SEM was calculated for 5 days before and after diet, respectively.

Gastrointestinal permeability

Before starting the diet and then after 24 days the gastrointestinal permeability was assessed using a triple-sugar-test. The test is based in principle on the measurement of the urinary excretion of orally administered nonmetabolized sugar probe molecules (12). Thereby

sucrose served as marker for gastroduodenal permeability (13) and the lactulose/mannitol ratio (permeability index, PI) for intestinal permeability (11).

After an overnight fast, each subject provided a pre-test urine sample. Then they drank a solution containing 20 g sucrose, 10 g lactulose, and 5 g mannitol dissolved in 100 ml water. Urine was collected over 5 h with sodium acid as preservative. Subjects went without food during the test but were allowed to drink water after 2 h. Total urine volume was recorded on completion of the test and a 10 ml aliquot was stored at minus 20°C until analysis.

For sample preparation the protein was removed with sulfosalicylic acid and the urine was desalted with Amberlite MB-3 resin in the acetate form. Using meso-erythritol and turanose as internal standards the sugars were separated, analyzed and quantified by HPLC with pulsed electrochemical detection (Dionex, Idstein, Germany); chromatography module: 250 × 40 mm Carbopac PA-1 column (Dionex); eluent 150 mmol NaOH; flow; 1 ml/min. Results were expressed as the percentage recovery of the ingested dose of the sugars.

Helicobacter pylori

Before the onset of the diet patients were tested serologically for a *H. pylori* infection by IgG/IgA enzyme-linked immunosorbent assay (Verion, Würzburg, Germany). No eradication therapy was performed during the study.

Statistics

Data were presented as means ± SEM. Differences in permeability data between control group and urticaria group or between subgroups of patients were tested using the *U*-test of Wilcoxon–Mann–Whitney, differences between data of different time points of the study were tested with the Wilcoxon–Wilcox test; $P < 0.05$ was considered as significant.

Results

Before diet

All patients showed moderate to severe spontaneous occurrence of wheals almost continuously. Two patients had additional angioedema.

Both gastroduodenal and intestinal permeability differed significantly between patients and controls (Fig. 1). In 49% of patients with urticaria gastroduodenal permeability was above the upper limit of normal, defined as $m + 2SD$ of the control group. Intestinal permeability was above the upper limit in 24% of the patients.

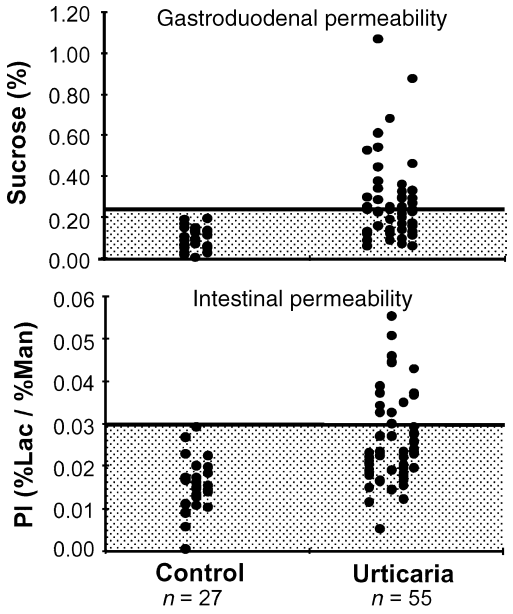

Figure 1. In the urticaria group both gastroduodenal and intestinal permeability were significantly higher than in the control group ($P < 0.001$). ▨ upper limit of normal: $m + 2SD$ control group.

Effects of diet

Skin symptoms. Response to the diet was defined as a lasting >50% reduction of the skin-symptom score during the period of the diet. According to this definition 29 patients were responders with a reduction of skin symptoms of more than 50% or even absence of skin symptoms in the last third of the dietary period (21.38 ± 1.06 before *vs* 4.72 ± 0.73 after diet). In contrast, in 26 patients there was no or only minor reduction of the skin symptoms (nonresponders, 18.69 ± 1.42 before *vs* 16.31 ± 1.30 after diet).

Gastrointestinal permeability. A subgroup analysis of the permeability data for the responders and the nonresponders revealed clear differences between the two groups (Fig. 2). Responders had a significantly higher gastroduodenal permeability even before the onset of the diet than the nonresponders (% sucrose: 0.36 ± 0.04 *vs* 0.15 ± 0.01; $P < 0.001$, *U*-test). While in the responder group the values decreased significantly with the diet (% sucrose: 0.36 ± 0.04 *vs* 0.17 ± 0.02; $P < 0.001$, Wilcoxon–Wilcox), there was no significant effect obvious in the nonresponder group (% sucrose: 0.15 ± 0.01 *vs* 0.16 ± 0.02). With respect to intestinal permeability the results were similar, however, they did not reach the level of significance (Fig. 2).

The sensitivity of the gastroduodenal permeability test, to predict response to the diet was 0.79. The specificity of the test, defined as the probability of a nonresponder to have a normal sucrose permeability, was 0.85.

H. pylori *status*. Seventy-seven percent of the CU patients were Hp negative. The distribution of Hp negative patients was not different between responder and nonresponder groups ($n = 19$ *vs* $n = 22$). Correspondingly 23% of the patients were Hp positive (eight responders *vs* four nonresponders). Gastroduodenal permeability was elevated in 44% of all Hp-negative patients and in 75% of all Hp-positive patients.

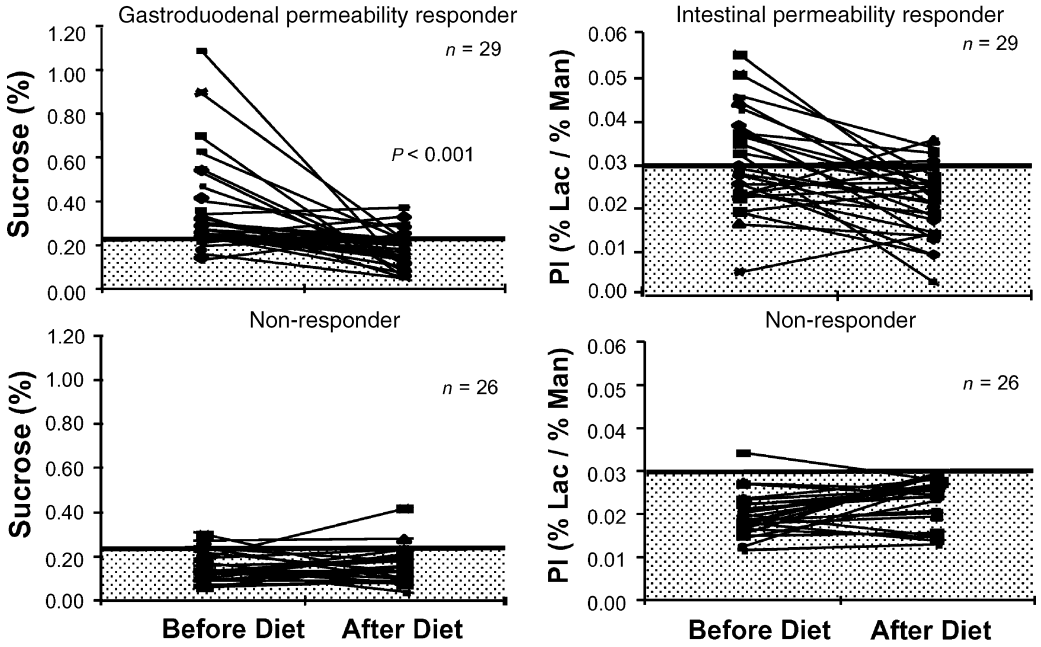

Figure 2. In the responder group gastroduodenal permeability before the diet was higher than in the nonresponder group ($P < 0.001$). In the responder group only, gastroduodenal permeability decreased with the diet ($P < 0.001$). The results for intestinal permeability tended to be similar, however, they did not reach the level of significance. ▨ upper limit of normal: $m + 2SD$ control group.

Discussion

The term 'pseudoallergy' or nonallergic hypersensitivity (1) is usually used for mechanisms in which the primary stimulus is nonimmunologic, i.e. not IgE mediated. The clinical symptoms of pseudoallergy closely mimic type I allergy, but there are distinct differences. In type I allergy, symptoms occur frequently with a latency of only some minutes and cease after omission of the allergen for more than 24 or 48 h. After the ingestion of pseudoallergens, however, symptoms occur frequently with a latency of more than 4 h and cease only after the omission of the suspected pseudoallergens for more than 10 to 14 days (14).

Diets low-in-pseudoallergens have been repeatedly shown to be useful in patients with CU (see overview in Table 1), however, up to date neither an *in vitro* skin test has been developed nor is there a convincing concept regarding the pathomechanism of urticaria elicited by pseudoallergens.

To our knowledge gastroduodenal permeability has not yet been adequately studied in patients with CU. Intestinal permeability data are also rare if not documenting the situation of an allergen provocation in known food allergy (11, 15) but dealing with baseline data only. In this context André et al. (15) reported a slightly elevated lactulose/mannitol index in CU patients, while in a study of Guida et al. (16) intestinal permeability was normal in all patients with CU. In the latter study, however, cellobiose was used as permeability marker and therefore a marker loss due to the intestinal cellobiase activity has to be kept in mind. In the present study, both gastroduodenal and intestinal permeability were elevated under basal conditions. But when correlating these data with the response of the skin symptoms to the diet low in pseudoallergens only the results for the gastroduodenal mucosa were significant. This stresses the importance of the barrier function of stomach and duodenum in this context. Gastroduodenal permeability was measured using sucrose as a marker substance. In 1993 the sucrose-permeability test was introduced as a novel, noninvasive method for determining a loss of barrier integrity of the gastroduodenal mucosa (13). Since then, the validity of the method has been confirmed repeatedly (17). Sucrose, being a disaccharide, passes the epithelium via the paracellular route (12), thereby reflecting tight junction permeability.

At present we cannot prove which role the documented barrier dysfunction plays in the disease process of pseudoallergic CU. With respect to the results of this study, it is obvious that only a subgroup of patients with CU responded to the elimination of pseudoallergens in their daily food, showing a normalization of mucosal permeability and skin symptoms. Therefore, it is likely that there is not only one, but multiple factors acting together and influencing the manifestation of the disease. Recently, one of the most discussed factors is a *H. pylori* infection of the gastrointestinal tract. Some studies have shown a high prevalence of *H. pylori* infection in patients with CU and occasional remission of the skin lesions after

eradication therapy (6, 18, 19). However, a considerable number of publications, including our study, have failed to find such a significant relationship between these conditions (8, 20). In addition, it is still controversial whether or not a *H. pylori* infection increases gastric permeability (21–23). The percentage of *Helicobacter* positive patients in the present study resembles the general prevalence in the German population (24, 25).

The present study for the first time shows a possible link between gastric impairment and pseudoallergy and suggests that the measurement of gastroduodenal permeability is a useful screening test to identify those patients who would profit from a diet low in pseudoallergens. The values for sensitivity and specificity of the test support this idea. In view of this good predictive value the possibility of introducing such a test into clinical practice should be discussed.

Also the fact that the impairment of a gastric mucosa barrier is reversible, points at a causal relationship. One of the major features of pseudoallergy is the fact that spontaneous remission of the disorder is common. Thus, in our own studies we have frequently observed that maintenance of a diet is only required for a period of weeks or a few months, thereafter normal food is tolerated again. This finding is also in line with data regarding acetylic salicylic acid (ASA) intolerance, the drug most frequently causing pseudoallergic reactions. The majority of ASA intolerance patients are free of symptoms on re-exposure to the drug 1 year later.

In summary, the results presented here indicate for the first time that an impaired gastroduodenal barrier function may be of pathophysiological importance in the development of pseudoallergy. Further studies are now required to investigate the underlying pathomechanism in detail.

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