Colorectal mucosal histamine release by mucosa oxygenation in comparison with other established clinical tests in patients with gastrointestinally mediated allergy

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Abstract

AIM: This study evaluated colorectal mucosal histamine release in response to blinded food challenge-positive and -negative food antigens as a new diagnostic procedure.

METHODS: 19 patients suffering from gastrointestinally mediated allergy confirmed by blinded oral provocation were investigated on grounds of their case history, skin prick tests, serum IgE detection and colorectal mucosal histamine release by ex vivo mucosa oxygenation. Intact tissue particles were incubated/stimulated in an oxygenated culture with different food antigens for 30 min. Specimens challenged with anti-human immunoglobulin E and without any stimulus served as positive and negative controls, respectively. Mucosal histamine release (% of total biopsy histamine content) was considered successful (positive), when the rate of histamine release from biopsies in response to antigens reached more than twice that of the spontaneous release. Histamine measurement was performed by radioimmunoassay.

RESULTS: The median (range) of spontaneous histamine release from colorectal mucosa was found to be 3.2 (0.1%-25.8%) of the total biopsy histamine content. Food antigens tolerated by oral provocation did not elicit mast cell degranulation 3.4 (0.4%-20.7%, \( P = 0.4 \)), while anti-IgE and causative food allergens induced a significant histamine release of 5.4 (1.1%-25.6%, \( P = 0.04 \)) and 8.1 (1.5%-57.9%, \( P = 0.008 \)), respectively. 12 of 19 patients (63.1%) showed positive colorectal mucosal histamine release in accordance with the blinded oral challenge responding to the same antigen(s), while the specificity of the functional histamine release to accurately recognise tolerated foodstuffs was found to be 78.6%. In comparison with the outcome of blinded food challenge tests, sensitivity and specificity of history (30.8% and 57.1%), skin tests (47.4% and 78.6%) or antigen-specific serum IgE determinations (57.9% and 50%) were found to be of lower diagnostic accuracy in gastrointestinally mediated allergy.

CONCLUSION: Functional testing of the reactivity of colorectal mucosa upon antigenic stimulation in patients with gastrointestinally mediated allergy is of higher diagnostic efficacy.

Key words: Gut; Histamine release; Mucosa oxygenation; Food allergy diagnostics; Gastrointestinally mediated allergy

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INTRODUCTION

Gastrointestinal complaints after the ingestion of certain foodstuffs often pose diagnostic problems in various clinical situations such as food hypersensitivity, enzyme deficiencies, irritable bowel syndrome, inflammatory bowel disease, dyspepsia, eosinophilic gastroenteritis and several others. However, identification of immunologically mediated food hypersensitivity at the gastrointestinal level remains problematic, since skin tests and allergen specific serum IgE detection (e.g. RAST) may fail to show clear signs of food-specific sensitisation and do not necessarily indicate symptomatic food allergy. This is also valid for functional tests using blood cells (basophil histamine, or leucotriene release), lymphocyte transformation tests or measurement of mediators in blood or serum. Oral provocation, referred to as the ‘gold standard’ for food allergy diagnosis, is both time consuming and cost intensive, may put the patient at a

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more or less severe risk, allows only one food to be tested per day, is often difficult to evaluate and is without doubt an unpopular and irritating procedure for the patient[1,5,8]. Consequently, different methodical approaches have emerged for the improvement and acceleration of the cumbersome diagnostic way to identify patients with food allergy primarily involving the gastrointestinal tract. Already in 1942, 1984 and 1997, direct endoscopic observation has repeatedly been claimed to be of diagnostic value for recognition of food allergy when antigenic solutions were applied to the intestinal mucosa[9-11]. However, direct endoscopic evaluation of allergen application and endoscopic or fluoroscopic balloon perfusion techniques harbour similar disadvantages to those experienced in oral provocation tests. All of these tests require special conditions with strict medical supervision because of the risk of allergic reactions in vivo during endoscopy or allergen perfusion[12-15]. Only a few allergens can be tested during one examination and, in case of an endoscopic allergen injection, the endoscopic procedure is prolonged by at least 20 min, providing a higher risk of procedure-related complications, bacterial translocation and discomfort to the patient[10-14]. Finally, the outcome of these endoscopic methods and the results obtained from double-blind, placebo-controlled food challenge procedures have never been directly compared on a scientific basis. Nevertheless, this is absolutely necessary for an appropriate evaluation in routine practice with respect to their diagnostic effectiveness[1,5,8].

Another possibility to identify food allergy at the gastrointestinal tract was described in 1989. Baenkler et al used endoscopically taken samples from the duodenum to show antigen-induced histamine release ex vivo[15,16]. Since many patients with suspected gastrointestinal mediated allergy (GMA) have to undergo endoscopic procedures for differential diagnostic reasons, this approach has the advantage that the principle demonstration of a food-induced mediator release can be performed outside of the patient, thus avoiding the risk of allergic reactions in vivo. In addition, several food antigens can be tested simultaneously without further burden to the patient[15-17]. However, performance of functional histamine release experiments requires certain laboratory equipment and, initially, should be compared with the 'gold standard' for food allergy diagnostics before introducing this approach into clinical practice.

Similar to Baenkler’s approach using duodenal mucosa, functional histamine release should also be expected from mucosa of other regions of the intestine[15-17], provided that these tissue samples contain large enough numbers of (mucosal) mast cells. However, ex vivo histamine release from viable tissue samples of the lower gastrointestinal tract in response to nutritive antigens has not yet been studied together with the standardised in vivo oral challenge tests in order to provide a direct comparison of the two diagnostic methods. For this reason, this study investigated the rate of histamine release from colorectal mucosal samples in a group of patients with proven food allergy and compared the results of ex vivo mucosa oxygenation with the outcome of standardised blinded oral provocation tests.

### Table 1 Patient data, allergens used for oral provocation, colorectal mucosal histamine release, skin prick test, serum IgE detection (RAST), and patient’s history

| Pat. No. | Sex | Age | Allergen | Oral provocation | Colorectal HR | Skin test | RAST IgE | H |
|----------|-----|-----|----------|------------------|---------------|------------|----------|---|
| 1WT F    | 44  | Cheese | + | + | - | - | + | ? |
| 2DF M    | 49  | House dust | + | + | + | + | + | ? |
| 3OL M    | 41  | Soy flour | + | + | + | + | + | + |
| 4CF M    | 23  | Rye flour | + | + | - | - | - | - |
| 5NA F    | 42  | Wheat flour | + | + | + | - | + | ? |
| 6IL M    | 43  | Wheat bran | + | + | + | - | - | ? |
| 7CG M    | 19  | Soy flour | + | + | + | + | + | + |
| 8JF F    | 25  | Soy lecithin | + | - | - | - | + | + |
| 9MR F    | Milk | + | + | - | - | - | - | - |
| 10MB F   | 23  | Wheat | + | + | + | + | + | + |
| 11FB F   | 51  | Wheat flour | + | + | + | + | + | + |
| 12RA M   | 38  | Spices | + | + | + | + | + | + |
| 13KF M   | 32  | Milk | + | + | + | + | + | + |
| 14AC F   | 40  | Nuts | + | + | + | - | - | - |
| 15KF M   | 38  | Nuts | + | + | + | - | - | - |
| 16FM M   | 28  | Nuts | + | + | + | - | - | - |
| 17SJ F   | 37  | Nuts | + | + | + | - | - | - |
| 18LS M   | 44  | Rice | + | + | + | - | - | - |
| 19SL M   | 29  | Wheat flour | + | + | + | - | - | - |

HR: histamine release; no.: number; pat.: patient; H: patients’ history with regard to causative allergens and tolerated foodstuff.

### MATERIALS AND METHODS

#### Patients

A total of 19 patients (7 male, 12 female; median age 38.0, range 19-51 years) were included in this study (Tables 1 and 2). All patients gave their informed consent and the study protocol was approved by the local ethics committee (No. 331). All patients (100%) reported abdominal symptoms, nausea, pain, vomiting and/or diarrhoea (98%) after certain meals, while postprandial extraintestinal signs of allergy such as skin reactions, asthma bronchiale and allergic rhinoconjunctivitis occurred only in a small percentage of patients (32%). Every patient was assessed about their history of non-tolerated foods, tests were conducted for basic foodstuff. Case history, skin test reactions and RAST results were then compared with the outcome of oral
of 5 mL of the full strength native allergen solution was followed by 1/10 of the dose 3 h later and finally, a dose dilution of the native allergen solution was administered, administered in three different doses. Initially, a 1/20 given to the patients via a nasogastric tube or orally, while all other allergens were freshly prepared and were used (Maser, Bochum, Germany). These were applied commercially available allergen solutions for skin tests. For provocation of flours (wheat, rye, soya, barley), oligopeptides (Survimed OPD, Fresenius, Germany) and placebo-controlled food challenge tests (BPCFC) adding challenge tests.

Food allergy was confirmed in each patient by blinded, placebo-controlled food challenge tests (BPCFC) adding the putative allergen to a basic diet containing rice, potato, oligopeptides (Survived OPD, Fresenius, Germany) and tea. For provocation of flours (wheat, rye, soya, barley), commercially available allergen solutions for skin tests were used (Maser, Bochum, Germany). These were applied orally, while all other allergens were freshly prepared and given to the patients via a nasogastric tube.

BPCFC was performed in a standardised fashion, while patients were hospitalised. Food antigen was administered in three different doses. Initially, a 1/20 dilution of the native allergen solution was administered, followed by 1/10 of the dose 3 h later and finally, a dose of 5 mL of the full strength native allergen solution was provided. One single food antigen was tested per day. Placebo consisted of an oligopeptide-diet (protein source: hydrolysed soybean, Survived OPD, Germany), which was also used for base-line nutrition (minimum: 1800 kcal/d), in conjunction with a rice-potato diet in order to prevent a catabolic state. A single blind challenge was performed in 42% (patients unaware of provocation protocol), while a double-blind challenge was carried out in 58% (patients and physicians unaware of the provocation protocol). Blinding of the food antigens was managed by nutritionists, who were responsible for the preparation and addition of the allergens to usually tolerated foodstuff or to the oligopeptide solution, respectively.

Physicians selected the type of food to be tested either on the basis of the patients' history, previous results of skin prick tests and RAST tests or from a list of basic foodstuff. During the provocation procedure, the patients were provided with a peripheral venous line, and all medical staff involved was trained for medical intervention in case of an anaphylactic reaction. For the definition of food allergic reactions, a modified scoring system for symptoms was applied and main symptoms of patients evoked by the food challenge are listed in Table 2.

Food hypersensitivity was diagnosed only when food-specific immune events were detected through positive skin tests (mean wheal diameter of 3 mm or greater than negative control [5,18,19]), serum RAST-IgE (> class II [8,19]) or through proof of intestinal IgE by endoscopically guided segmental lavage [18,19] in conjunction with a reproducible clinical adverse reaction to the food antigen(s) applied [1,9,18,19]. During BPCFC, at least one reproduction of an allergen induced clinical reaction and one or two placebo challenges were included for every patient. Whenever possible, both antigens causing clinical symptoms as well as tolerated antigens were applied to the patient, or else investigated on grounds of case history, skin tests, RAST and mucosal histamine release. In this way, a provocation allergen and a control allergen (Table 1) was determined for most patients (14 of 19 patients 74%), which enabled the direct comparison of the mucosal histamine release results with those of the BPCFC.

Before the execution of food challenge tests, additional examinations including endoscopy and histology of the upper and lower gastrointestinal tract were conducted [5,18-20].

Patients with macroscopic alterations of the mucosa or with histological signs of acute inflammation (Crohn's Disease, ulcerative colitis at) were excluded from the study as well as those suffering from other digestive diseases (e.g. celiac disease, autoimmunopathy, mastocytosis, eosinophilic gastroenteritis etc).

At least two weeks in advance of colonoscopy and BPCFC, any antiallergenic, immunosuppressive or steroid treatments had been discontinued for all patients. Patients were prepared for colonoscopy using a commercial polyethyleneglycol solution. To facilitate colonoscopy, benzodiazepins (midazolam, diazepam) and meperidine were used at a dose of 2.5-10 mg (midazolam, diazepam) and 25-150 mg (meperidine), respectively [20,21].

### Colorectal mucosal histamine release

For colorectal mucosal histamine release by mucosa
oxygenation, 138 samples from the left-sided colon were obtained from all 19 patients. In 14 of 19 patients (74%), 10-12 mucosal samples were taken during colonoscopic examination. Whenever possible, 8 biopsies (4 repeats) were used for mucosa oxygenation and 2-4 for histological examination. The biopsies were immediately placed into a portable mucosa oxygenator (Intestino-Diagnostics, Erlangen, Germany) containing tubes filled with 2000 µL of oxygenated Hank’s solution (pO2: 85-95 mmHg, pH 7.0, 37ºC)\[16,17,20\]. Each incubation medium was bubbled with a steady flow of room air to ensure sufficient oxygen pressure inside the biopsy, to facilitate allergen distribution into the tissue or mediator release from the tissue and to avoid ischemic damage of the tissue\[16,17,20\].

Histamine release into the culture medium was measured at 0, 7.5, 15, and 30 min by removal of 200 µL of the supernatant at each sampling time\[17,20,21\]. To obtain as accurate histamine measurements as possible, each 200 µL sample was immediately denatured by heating to 95ºC for 5 min in order to destroy all histamine metabolising enzymes that may have been contained within the drawn supernatant\[17,20,21\].

Allergen induced histamine release was achieved by addition of 200 µL Hank’s solution containing 5 µL of native allergen solution to the culture medium at the sampling time of 0 min, thus providing a final concentration of 0.01 µg allergen/mL. The same procedure was applied for positive control using anti-human immunoglobulin E except that 20 µL of pure anti-IgE solution (Behringwerke, Marburg, Germany) were used for dilution. The final concentration of anti-human-IgE was 0.01 µg/mL, which has previously been found to be the optimal stimulation concentration\[16,17\]. For negative control (spontaneous mucosal histamine release), only 200 µL Hank’s solution were added to the culture medium. The stimulation procedure of the 8 samples of each patient was arranged as follows: two samples were studied for spontaneous mucosal histamine release (negative control), two for anti-IgE induced histamine release (positive control), two for a BPCFC-positive allergen (provocation allergen) and two for provocation negative, i.e. tolerated antigens (control allergen).

After a stimulation period of 30 min, the rest of the volume of 1400 µL containing the biopsy (1200 µL Hank’s + 200 µL stimulus) was also heated to 95ºC for five minutes in order to determine the remaining tissue histamine content and to denature tissue histamine catalobolising enzymes\[17,20,21\].

Histamine measurement

Histamine was measured using a sensitive and specific radioimmunoassay (Histamine RIA, Beckman-Coulter, Krefeld, Germany)\[17,21,22\]. The actual rate of histamine release was expressed as the percentage of the total tissue histamine content of the biopsy. This was calculated from the discharged histamine into the supernatant and the remaining histamine content in the tissue at the sampling time of 30 min\[17,20,21\]. Intra-assay and inter-assay coefficients of variation for the histamine radioimmunoassay (n > 150 samples) were 6.2% and 8.8% for supernatants, and 13.7% and 18.2% for detection of the remaining tissue histamine content, respectively. The individual rates of histamine release were found to vary by up to 24.0% within the same person.

Histamine content was also measured in native allergen solutions to exclude histamine contamination.

Statistical analysis

From each patient, two rates of histamine release were obtained for each of the parameters spontaneous histamine release, anti-IgE, provocation and control allergen. The average value for each pair of release data was calculated and used for final statistics as listed in Table 3.

For descriptive statistics of the whole group, the median and range were chosen. Statistical comparisons were made using the U-test (Wilcoxon, Mann & Whitney) and significance levels are given in brackets. For comparison of the clinical tests, ex vivo biopsy stimulation by mucosa oxygenation was considered successful (positive) when the antigen containing solution caused an increase of the histamine release up to more than twice that of the spontaneous release.

RESULTS

Histamine release from colorectal tissue

Spontaneous histamine release from viable colorectal mucosal fragments amounted to only 3.2% of the total tissue histamine content, indicating that mast cells are able...
to maintain their normal metabolism and their mediators
within granules during mucosa oxygenation (Table 3).
Application of anti-human-IgE induced a clearly enhanced
rate of histamine release of 5.4% \((P = 0.04)\) within 30
min, confirming the functional reactivity of mucosal
immune effector-and intestinal mucosal mast cells towards
IgE-receptor cross-linking\(^{[15,17,21,23]}\). Four of 17 patients
(23.5%) were found to be unresponsive to the anti-IgE
concentrations used. Interestingly, these patients had the
highest rates of spontaneous histamine release, possibly
indicating that mast cells had already been degranulated or
that a high rate of spontaneous histamine secretion may
exert some negative feed-back mechanisms on mast cell
triggering by anti-IgE (Table 3).

Incubation of intact colorectal tissue with BPCFC-
negative food antigens did not induce a significant increase
in histamine release (median increase 1.2 fold; range
0.6-4.4 fold of spontaneous mediator release) in patients
with GMA. Histamine release with control antigens
amounted to 3.4% and was not statistically different from
spontaneous histamine release (Table 3).

In contrast, provocation allergens that evoked clinically
significant reactions in allergic individuals (BPCFC-positive
food antigens) already induced a 2.6 fold increased rate
of histamine release compared to the spontaneous release
(range 0.9-24 fold) during 30 min of mucosa oxygenation.
The percentage of histamine release in response to
provocation allergens was 8.1% and significantly different
from spontaneous histamine release \((P = 0.008)\).

**Colorectal mucosal histamine release in comparison with
established clinical tests**

Colorectal mucosal histamine release was positive in 12 of
19 patients (sensitivity 63.1%, Table 4), who experienced
a reproducible clinical reaction in response to the same
provocation antigen. In contrast, 3 of 14 patients (21.4%
false positive) discharged significant histamine amounts
although oral provocation was negative. Control antigens,
tolerated by the patient during BPCFC, were also found
to be negative with regard to histamine release in 11 of 14
patients (specificity 78.6%).

When comparing established clinical parameters for
food allergy diagnostics with the outcome from blinded
provocation tests (gold standard), a lower diagnostic
accuracy was obtained through reference to patients’
history (Table 5), skin test results (Table 6) and allergen-
specific IgE detection in serum (Table 7) than with
histamine release experiments.

The comparison between patients’ history and
BPCFC (Table 5) was somewhat impeded, since only
13 of 19 patients (68.4%) knew their allergen inducing
clinical symptoms, 7 of 14 patients (50%) with recurrent
gastrointestinal complaints tried to give exact answers on
questions about their well tolerated foods, while all other
individuals had significant uncertainties about adverse
reactions to or tolerance of the food antigens tested.

**DISCUSSION**

Diagnosis and existence of gastrointestinal food allergy
are still a matter of debate\(^{[1,4,5,18]}\). To date, no exact
diagnostic and practical relevant means are readily
available for the gastroenterologist or endoscopist to
examine the gastrointestinal mucosa for signs of food
hypersensitivity, when patients with recurrent episodes
of variable gastrointestinal complaints are referred for
further diagnostics\(^{[1,8,10]}\). One innovative approach for the
diagnosis of food hypersensitivity by endoscopy may be
the use of a mucosa oxygenation system, which allows
culturing of small viable endoscopic samples outside of

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**Table 4** Colorectal mucosal histamine release in comparison with the outcome of oral provocation tests in patients with GMA

|            | Positive HR | Negative HR | Line sum |
|------------|-------------|-------------|----------|
| Positive BPCFC | 12          | 7           | 19       |
| Negative BPCFC | 3           | 11          | 14       |
| Column sum   | 15          | 18          |          |

**Table 5** Patients’ history in comparison with the outcome of oral provocation tests in patients with GMA

|            | Positive H  | Negative H | Line sum |
|------------|-------------|------------|----------|
| Positive BPCFC | 4          | 9          | 13       |
| Negative BPCFC | 3          | 4          | 7        |
| Column sum   | 7           | 13         |          |

**Table 6** Skin prick tests in comparison with the outcome of oral provocation tests in patients with GMA

|            | Positive prick test | Negative prick test | Line sum |
|------------|---------------------|---------------------|----------|
| Positive BPCFC | 9                 | 10                  | 19       |
| Negative BPCFC | 3                 | 11                  | 14       |
| Column sum   | 12                  | 21                  |          |

**Table 7** Allergen-specific serum IgE determinations (RAST test) in comparison with the outcome of oral provocation tests in patients with GMA

|            | Positive RAST | Negative RAST | Line sum |
|------------|---------------|---------------|----------|
| Positive BPCFC | 11            | 8             | 19       |
| Negative BPCFC | 7             | 7             | 14       |
| Column sum   | 18            | 15            |          |
the patient for immunological release experiments. Since histamine is one important and very early secreted mediator of different types of IgE and non-IgE mediated allergic reactions, this study was designed to evaluate colorectal mucosal histamine release from patients with gastrointestinal food hypersensitivity. In contrast to allergic individuals with typical extraintestinal signs of type I food hypersensitivity, diagnostic problems have been repeatedly reported in this patient population primarily involving the gastrointestinal tract with symptoms of allergic diarrhoea, vomiting, nausea, etc. In addition, the frequency of local gastrointestinal allergy in several important clinical conditions is also still unclear.

This study demonstrates that a significant histamine release can be induced from colorectal mucosa upon IgE receptor cross-linking or antigenic stimulation ex vivo by mucosa oxygenation using endoscopically taken samples. This confirms that functional antigen-specific tests using histamine as the primary test parameter are equally feasible with mucosa from the lower gastrointestinal tract as from the upper gastrointestinal tract (duodenum) or more long-lived mediators like mast cell tryptase or eosinophilic cationic protein. However, in contrast to previously published work featuring tryptase or eosinophilic cationic protein, histamine release tests using biotomic tissue bear the distinct practical advantage that they can be performed within a short period of time of only 30 min, providing the appropriate technique to rapidly destroy all histamine catabolising enzymes in the drawn culture supernatants is applied. The quick performance of mucosa oxygenation using histamine as a diagnostic parameter may qualify this test for its use in clinical practice, possibly as a refinement or complement of existing endoscopic-diagnostic procedures when patients with suspected gastrointestinal food allergy are being referred for diagnostic work-up.

Compared to other human tissues or isolated mast cells, histamine release from colorectal mucosa was found to be of a smaller magnitude than expected. This could be a result of the short cultivation period and of the fact that colorectal tissue harbours large quantities of histamine metabolising enzymes, which are still active within the viable cultured tissue at a physiological rate during mucosa oxygenation. However, compared with the spontaneous rate of histamine release, functional mast cell stimulation by anti-IgE or BPCFC-positive antigens achieved a significantly higher rate of histamine release, while control antigens showed a similar degree of histamine release as the spontaneous secretion. This study proved unambiguously the reactivity of histologically normal gut mucosa in allergic patients upon specific challenge. In view of that, gastroenterologists will find a valuable addition to their diagnostic methods through the establishment of a functional test using biopsies of the involved and reacting allergic shock organ. Depending on the number of biopsies taken during endoscopy, this functional test allows the simultaneous examination of different food antigens during mucosa oxygenation. In this way, any contact between the antigen and the patient’s immune system is avoided and the patient is not put at risk of any allergic symptoms or reactions.

Although only a small group of patients was investigated in this study, colorectal mucosal histamine release was found to yield a diagnostic sensitivity and specificity of 63.1% and 78.6%, while skin tests and serum IgE detection reached only a sensitivity and specificity of 47.3% and 78.6% or 57.5% and 50%, respectively. Similar low rates of diagnostic accuracy of the skin prick tests and RAST tests have also been reported by other investigators in GMA.

This may be explained by the fact that sensitisation in the cutaneous and serological compartment may not always accurately reflect the immunological response of the mucosal microenvironment at the large surface area of the gastrointestinal tract. The presence of different (immunological) compartments with separate mechanisms for local IgE production in food hypersensitivity may also account for the known multitude of allergic manifestations in food allergy. This is illustrated by the fact that several individuals in this study experienced significant clinical symptoms during BPCFC despite negative skin or serum IgE tests, confirming the need for further diagnostic means directly targeting the involved shock organ.

Mucosa oxygenation with histamine or more long-lived mediators bears the potential to predict the outcome of double-blind, placebo-controlled food challenges. Hence, a future cost-effective approach of the gastroenterologist to diagnose gastrointestinal food allergy could possibly be based on the additional use of gut mucosal histamine release (Table 4) to avoid time-consuming, cost-intensive and sometimes risky challenge procedures. However, the real value of such a diagnostic procedure has yet to be established within greater patient populations. The rationale of this proposal for future diagnostics is given by the fact that gut mucosal histamine release was proven to be of superior diagnostic value compared to that of the commonly used allergological means such as case history, skin prick tests or RAST tests, as these are not always concise or do not directly examine the involved organ in patients with GMA, respectively. The data presented here suggest that patients with a food antigen-induced mucosal histamine release exceeding more than twice the amount of the spontaneous one be could directly subjected to a specific elimination diet.

As part of appropriately provided health care, prospective long-term analysis of the clinical course of these patients is always necessary. Diminishing financial resources, however, dictate the need for more economical investigations, which may be sufficed by mucosa oxygenation. Although this approach is more invasive than blinded food challenges, it needs only one endoscopic examination with testing of several antigens, while DBPCFC needs at least one (in-patient) test day for each individual allergen application. The data presented here suggest that mucosa oxygenation could perhaps eliminate the need to perform DBPCFC in a significant number of patients suspected of having GMA.

However, the fact that colorectal mucosal histamine release by mucosa oxygenation did not identify all BPCFC-positive allergens is more likely to be related to the
complex pathophysiology and compartmentalisation of gastrointestinal food allergy rather than to inadequately applied methods. Patients with positive provocation but negative colorectal histamine release, which was the case for 7 of 19 patients (36.8%), may develop their allergic reactions in more proximal parts of the gastrointestinal tract (e.g. stomach, duodenum). Or else, these patients may react only in blood or at extraintestinal sites, respond to the tested antigen mainly with other mediators rather than with histamine (e.g. arachidonic acid products, eosinophilic proteins et al) or may have produced the antigenic epitope after passage through the liver1,3,10,18,23,29. Conversely, control allergens, which elicited a significant histamine release in 3 of 14 patients (21.4%), may fail to provoke a clinically significant reaction unless histamine catabolism is sufficiently active1,18,23. In addition, the demonstration of food-specific histamine release from colorectal mucosa may also explain why some patients experience postprandial extraintestinal symptoms (urticaria, hypotension, asthma bronchiale et al) despite negative skin tests. In such cases, intestinally produced and released histamine may reach peripheral extraintestinal organs and activate their histamine receptors inducing classical extraintestinal allergic symptoms without the presence of food-specific IgE in the periphery. These different pathophysiological parameters in combination with several yet unknown or ill-defined factors (e.g. neurovegetative impulses, gut flora et al) contribute to or induce the great variability of clinical manifestations in GMA1,3,5,10,18,23,29.

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