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Protective Effects of Oral Disodium Cromoglycate on the Asthmatic Responses Induced by Food Allergy

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Abstract

Background: The food allergy can also participate in the pathological mechanism underlying the bronchial asthma. This should ultimately be confirmed by food ingestion challenge combined with monitoring of lung function (FVC and FEV_1), demonstrating the particular types of asthmatic response to ingested foods. The oral disodium cromoglygate (DSCG, Nalcrom®) has been shown to be effective drug in prevention of food allergy.

Methods: In 62 randomly selected patients with bronchial asthma developing 62 asthmatic responses to food ingestion challenge (17 immediate, IAR, $p<0.01$; 21 late, LAR, $p<0.001$; 8 dual late, DLAR, $p<0.05$; 11 delayed, DYAR, $p<0.05$; and 5 dual delayed DDYAR, $p<0.05$), the food ingestion challenges have been repeated twice, after the pretreatment with oral DSCG and after pretreatment with oral placebo. The study was performed according the double-blind, placebo-matched, cross-over design.

Results: The DSCG, administered orally in a daily dose of 4×200 mg starting 2 weeks before and continuing through the challenge day up to 3 days after the challenge, as compared with placebo, protected highly significantly the IAR ($p<0.001$), and the LAR ($p<0.001$), protected distinctly significantly the DLAR ($p<0.01$) and significantly the DYAR ($p<0.05$) and DDYAR ($p<0.05$). However, the distribution of the protective effects of oral DSCG on the particular types of asthmatic response to ingested foods has varied. The oral placebo was fully ineffective ($p>0.2$). No differences in the DSCG protective effects were observed with respect to the individual foods ($p>0.2$).

Conclusions: It can be concluded that the food allergy can causally be involved in some patients with bronchial asthma, resulting in development of various types of asthmatic response. The asthmatic responses to food ingested can effectively be prevented by pretreatment with disodium cromoglycate administered orally in a daily dose of 4x 200 mg. If necessary the treatment with oral DSCG can be combined with other treatments, such as elimination diet and/or other additional drugs, e.g. β_2–sympathomimetics or other drugs.

Keywords: Bronchial asthma; Food allergy; Food ingestion challenge; Types of asthmatic response to food ingested; Oral disodium cromoglycate

Abbreviations: DSCG: Disodium Cromoglycate; BPT: Bronchial Provocation Test; SPT: Skin Prick Test; BU: Biologic Unit; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Value in 1 Second; IAR: Immediate (Early) Asthmatic Response; LAR: Late Asthmatic Response; DLAR: Dual Late Asthmatic Response (a combination of IAR and LAR); DYAR: Delayed Asthmatic Response; DDYAR: Dual Delayed Asthmatic Response (a combination of IAT and DYAR)

Introduction

Food allergy is a multifactorial clinical manifestation of an immunological process in which foods, their parts and/or components act as antigens, stimulating the production of specific antibodies against them self or sensitizing the particular T-lymphocyte subset(s) and subsequently interacting with them [1-18]. Food allergy was classically attributed to the immediate (IgE-mediated) hypersensitivity mechanism(s) [1-5,8-12]. Nevertheless, later evidence has been found for the possible involvement of also other, so-called non—IgE-mediated, hypersensitivity mechanism types, such as late (immune-complex-mediated) and delayed (cell-mediated) types of hypersensitivity in food allergy [7-10,12-17,19-37]. Food allergy can be involved in various disorders of the respiratory tract, such as bronchial asthma, allergic rhinitis, sinusopathy, etc [1-3,6-10,12-17,19-21,23-25,38-42]. This involvement can occur either in a primary form, where the foods act as the sole causal factor in this disorder, or in a more frequently occurring secondary form, wherein addition to the already existing bronchial asthma to inhalant allergens, the foods play an additional role [6,7,19,23-25,43]. The involvement of food allergy in patients with bronchial asthma leads to the development of various types of asthmatic response, such as immediate/early (IAR/EAR), late (LAR), dual late (DLAR, a combination of an immediate and a late response),delayed (DYAR) and dual delayed (DDYAR, a combination of an immediate and a delayed) responses, described in our previous papers and reported also by other investigators [7,8,12-14,16,17,19-21,23-25,27-35,37,38,44-46]. The particular types of asthmatic response to food ingestion challenge differ each from other with respect to their clinical features, the association with other diagnostic parameters and the possibly underlying immunologic mechanisms [7,9-15,19-35,38,47-54]. The provocation tests with foods should be considered to be definite confirmation of the involvement of the certain foods in the patient's complaints, e.g. bronchial asthma [1-12,14-16,19-21,23-25,30,31,37-40,41,44-64]. Unfortunately the role of food allergy in patients with bronchial asthma is still underestimated by the clinicians because: (a) there is a the dearth of information

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concerning this problem; (b) the involvement of food allergy in patients with allergic disorders is complex, has various forms and modifications; (c) the diagnostic procedure(s) and confirmation of the in allergy in the patient's complaints is not an easy process, it requires specific conditions and precautions and is not performed in all clinics [1-12,14-16,19-21,23-25,30,31,37-40,41,44-64]. The management of the bronchial asthma due to the food allergy is usually limited to the elimination diet, symptomatic treatment with the H1-sometimes also H2-receptor antagonists, anticholinergics, beta-2-sympathomimetics and sometimes inhalant corticosteroids.

Disodium cromoglycate (DSCG) administered orally and its possible protective effects on various clinical manifestations and forms of food hypersensitivity have already been discussed in the literature, through sometimes from controversial points of view [2,5,7,8,15,24,41-43,65-75]. Nevertheless, we were unable to find any report in the literature available concerning the investigation of protective effects of disodium cromoglycate on the particular asthmatic response types due to the food allergy in a sufficiently large, representative and well-diagnosed group of asthmatics. The purpose of this study, being a continuation of our previous preliminary work, was to investigate the possible existence of significant protective effects of disodium cromoglycate. (Nalcrom®) on the basic types of asthmatic response to food ingestion challenge in patients with bronchial asthma, and to define the indications for the practical use of this drug in patients suffering from bronchial complaints due to the food ingested/food allergy.

Materials and Methods

Patients

Sixty-two patients with bronchial asthma in whom the food allergy was suspected to play a role, who had been referred to our Department of Allergology and Immunology (Institute of Medical Sciences "De Klokkenberg", Breda, The Netherlands) during 1999-2000 for more extensive diagnostic analysis, and developing asthmatic response to ingestion challenge with certain foods, have volunteered to participate in this study.

These patients 18-52 years of age, included 47 subjects with already existing bronchial asthma to inhalant allergens, in whom the suspected food allergy participated additionally in their bronchial complaints (Group I) and 15 subjects in whom the food allergy was suspected to be the sole cause of their bronchial complaints (Group II) (Table 1).

These patients reported suspect/positive history for one or more foods (81%), positive skin (prick and/or intracutaneous) tests with various food extracts (88%) and some of them also showed positive specific IgE antibody for some foods (Tables 1-4). They had no history of anaphylactic reactions did not suffer from any airway infections or any systemic or serious disorder, did not use oral corticosteroids or immunotherapy and the pregnancy has been excluded. They all demonstrated negative lactose intolerance test. The patients were examined by means of routine diagnostic procedure, serving also as an exclusion- inclusion check i.e. confirmation of a patient 's eligibility for the study and the exclusion of contraindications [4,6-8,10,11,19,20,23-25,39,41,45,47-49,51-58,60,61,63,64].

This procedure consisted of: (1) the general part: disease history, physical examination, basic laboratory tests, X-ray of chest and sinuses, lung function, determination of blood gases and bacteriological examination of the sputum; (2) the allergologic part: skin tests with inhalant and food allergens, bronchial histamine threshold [61,75-79], and determination of the serum immunoglobulins; (3) 109 bronchial challenges with inhalant allergens (BPT) [75-79] and (4) 97 ingestion challenges with selected foods, suspected from the history and/or skin tests, in combination with recording of the lung function (FVC and FEV_1). A 7-day interval was always inserted between the consecutive tests, to prevent carry-over effects. All challenges were performed during a period without manifest symptoms and during a short hospitalization of the patient under standard conditions. The particular food used for the challenges has always been avoided for 4 weeks before the challenges.

Inhaled glucocorticosteroids (n=27) and long-acting β_2–symphatomimetics (n=55) were withdrawn 4 weeks, inhaled cromolyn (n=19), inhaled nedocromil (n=11) and leukotriene modifiers (n=4) 2 weeks and other treatments 48 hours before each of the challenges. If the FEV_1 or both the FVC and FEV_1 values decreased after the allergen challenge and/or food ingestion challenge by 50% or more, with respect

	Patients							
	Total n=16	**IAR n=17**	**LAR n=21**	**DLAR n=8**	**DYAR n=11**	**DDYAR n=5**	**NAR n=35**	**Control subjects n=15**
Group I/II	47/15	14/3	13/8	5/3	8/3	3/2	19/16	
Age (years)	29 ± 5	24 ± 3	30 ± 4	35 ± 6	26 ± 4	25 ± 2	28 ± 7	31 ± 4
Gender (M/F)	29/33	8/9	9/12	4/4	6/5	2/3	16/10	7/8
Disease history (years)	5.1 ± 0.6	5.0 ± 1.0	4.7 ± 1.0	5.5 ± 1.4	5.6 ± 0.9	4.8 ± 0.7	5.9 ± 1.8	4.5 ± 1.2
FEV1 (% predicted)	96 ± 5	94 ± 3	98 ± 2	95 ± 6	97 ± 3	93 ± 6	95 ± 3	97 ± 2
FVC (% predicted)	99 ± 2	98 ± 4	100 ± 3	98 ± 5	103 ± 4	99 ± 3	104 ± 2	98 ± 3
Blood leukocyte count ($\times 10^9$/L)●	8.0 ± 0.78	8.3 ± 1.0	7.8 ± 0.5	6.9 ± 1.0	9.1 ± 0.5	9.1 ± 0.5	8.1 ± 1.3	7.9 ± 0.6
Blood eosinophil count ($\times 10^6$/L)●●	355 ± 52	389 ± 44	334 ± 27	392 ± 53	257 ± 19	288 ± 22	263 ± 13	413 ± 69
Blood neutrophil count ($\times 10^9$/L)●●●	5.4 ± 0.6	4.9 ± 0.8	5.6 ± 0.4	4.8 ± 1.1	5.1 ± 1.0	6.9 ± 0.5	5.5 ± 0.7	5.3 ± 0.8
Bronchial histamine threshold (BHT)□								
≤ 2.0 mg/mL	4	2	1	0	1	0	8	2
4.0 mg/mL	7	1	2	1	1	2	10	6
8.0 mg/mL	6	2	1	2	0	1	9	5
16.0 mg/ml	9	3	2	2	1	1	6	1
32.0 mg/ml	14	3	3	3	4	1	2	1
>32.0 mg/mL	22	6	12	0	4	0	0	0

Values=mean ± SD; ●=normal value=4.0-10.0$\times 10^9$/L; ●●=normal value=<300$\times 10^6$/L; ●●● normal value=2.0-7.2$\times 10^9$/L; □=normal value ≥ 32.0 mg/mL [76-79,81,82]

Table 1: Clinical characteristics of the patients and control subjects.

Foods	Total n=16	Amount ingested	IAR n=17	LAR n=21	DLAR n=8	DYAR n=11	DDYAR n=5	NAR n=35
Milk	10	100 mL	3	3	1	2	1	4
Cheese	7	100 g	2	2	0	2	1	3
Chocolade	6	50 g	2	2	1	1	0	3
Peanuts	4	20 g	1	1	0	1	1	1
Almonds	2	20 g	0	1	0	1	0	4
Hazelnuts	3	20 g	1	1	0	1	0	3
Cashews	1	20 g	0	0	0	1	1	2
Walnuts	1	20 g	0	1	0	0	0	0
Shrimps	6	50 g	2	2	1	0	1	1
Haring	1	100 g	0	1	0	0	0	1
Eggs	2	30 g	0	0	1	1	0	2
Tomato	3	100 g	1	1	1	0	0	2
Lettuce	1	100 g	0	1	0	0	0	1
Onion	3	10 g	2	1	0	0	0	2
Garlic	2	5 g	0	1	1	0	0	1
Horseradish	1	50 g						0
Banana	2	100 g	1	0	1	0	0	1
Apple	3	100 g	1	1	0	1	0	2
Peer	1	100 g	0	1	0	0	0	0
Pork	2	50 g	1	1	0	0	0	0
Lamb	1	50 g	0	0	1	0	0	1
Sherry	1	20 mL	0	1	0	0	0	1

Table 2: Foods caused particular types of asthmatic response.

	Patients							
	Total n=62	IAR n=17	LAR n=21	DLAR n=8	DYAR n=11	DDYAR n=5	NAR n=35	Control subjects n=15
Positive SPT response◊								
- immediate	15	8	3	4	0	0	9	0
Negative SPT response ◊	47	9	18	4	11	5	26	15
Positive i.c.test response ◊ ◊	55	15	18	7	10	5	34	14
- immediate	23	11	6	3	2	1	6	5
- late	22	4	12	4	1	1	23	9
- delayed	10	0	0	0	7	3	5	0
Negative i.c. test response ◊ ◊	7	2	3	1	1	0	1	1
Increased total IgE (serum)	4	2	2	0	0	0	3	0
Positive specific IgE (serum)□□□	9	5	3	1	0	0	1	1
Increased total IgG (serum)●	5	2	2	1	0	0	1	0
Increased sub-classes (serum)●●								
- IgG1	1	0	1	0	0	0	0	0
- IgG2	0	0	0	0	0	0	0	0
- IgG3	2	1	1	0	0	0	0	0
- IgG4	2	1	0	1	0	0	0	0
Increased total IgM (serum)●●●	0	0	0	0	0	0	0	0
Increased total IgA (serum)	3	1	1	2	0	0	0	0
Concomitant disorders								
- allergic rhinitis	9	3	3	2	1	0	1	1
- atopic eczema	17	5	8	2	1	1	0	2
- urticaria	3	0	1	2	0	0	0	0
- angio-neurotic edema	1	0	0	1	0	0	0	0
- gastrointestinal complaints	21	9	10	1	1	0	0	0

IAR:Immediate Asthmatic Response; LAR: Late Asthmatic Response; DLAR: Dual Late Asthmatic Response (immediate+late); DYAR: Delayed Asthmatic Response; DDYAR: Dual Delayed Asthmatic Response (immediate+delayed); NAR=NegativeAsthmatic Response; ◊=Skin Prick Test (SPT); ◊ ◊=intracutaneous (intradermal) skin tests; □□= total IgE in the serum (PRIST) normal value=<500 IU/mL; □□□= positive allergen-specific IgE in the serum for the particular (tested) food (ImmunoCAP) ≥ 0.70 U/mL (=more than class 1); ●= total IgG in the serum (Single radial immunodiffusion and ELISA)-normal value ≤ 15.0 g/L; ●●=normal values: IgG1<5.0 g/L, IgG2<2.6 g/L, IgG3<0.4 g/L, IgG4<0.5 g/L; ●●●=IgM ≤ 3.8 g/L; ■=IgA ≤ 4.0 g/L;

Table 3: Survey of other diagnostic parameters.

to the predicted values, the patients (n=3) were treated with a single dose of 400 µg salbutamol aerosol. The local ethical committee (IRB-MCK) approved the study and informed consent was obtained from all study participants. The study was conducted according to the WMA Declaration of Helsinki concerning the principles for medical research involving human subjects.

	History + Skin +	History ± Skin +	History + Skin -	Total
- 62 positive responses	46 (74%)	9 (15%)	7 (11%)	62 (100%)
- 35 negative responses	6 (17%)	21 (60%)	8 (23%)	35 (100%)
Total	54 (55%)	30 (30%)	15 (15%)	97 (100%)

+ =positive; ± =unknown; - =negative

Table 4: Agreement between disease history and skin tests.

	Patients						
Bronchial Complaints	**IAR n=17**	**LAR n=21**	**DLAR n=8**	**DYAR n=11**	**DDYAR n=5**	**NAR n=35**	**Control subjects n=15**
Dyspnea							
--	0	0	0	0	0	97	100
+	12	5	12	0	20	3	0
++	53	71	38	73	40	0	0
+++	35	24	50	27	40	0	0
Wheezing							
--	0	0	0	0	0	94	93
+	0	10	38	0	40	3	7
++	47	43	12	45	40	3	0
+++	53	47	50	55	20	0	0
Cough							
--	6	4	63	9	40	100	100
+	6	29	13	0	20	0	0
++	41	29	24	27	40	0	0
+++	47	38	0	64	0	0	
Expectoration							
--	83	76	100	9	100	100	100
+	17	24	0	91	0	0	0

Bronchial complaints (author's modified score system): --=absent , +=slight, ++=moderate/intermittent, +++=pronounced /regularly

Table 5: Survey of bronchial complaints during the asthmatic response types to food ingestion (in %).

Allergens

Dialyzed and lyophilized allergen extracts of inhalant allergens as well as of foods (Allergopharma, Reinbek, Germany) diluted In PBS (phosphate-buffered saline) were used in concentrations of 50-500 BU/mL for skin tests and in concentrations of 1000-3000 BU/mL for bronchial challenges (BPTs). The concentrations recommended by the manufacturer were 100-500 BU/mL for skin prick as well as intradermal tests (SPTs) and 5000 BU/mL for the BPTs.

Skin tests

The skin prick tests (SPTs) in concentration of 500 BU/mL were performed and evaluated after 20 minutes and again after 24 hours. If the SPT were negative, than intracutaneous (intradermal) tests in concentrations of 100 BU/mL and 500 BU/mL were carried out and evaluated 20 minutes, 6, 12, 24, 36, 48, 72 and 96 hours after the injection [6,7,19,20,23-25,40,43,61,76-80]. If the SPTs were positive (early/immediate skin response), then the intracutaneous tests were performed in concentrations of 200 BU/mL and evaluated up to 96 hours after the injection. Histamine diphosphate was used as a positive, whereas PBS as a negative control. A skin wheal (>7.0 mm in diameter) appearing within 20 minutes after the injection was considered to be a positive immediate skin response, the skin infiltration observed between 6-12 hours to be a late skin response and the skin in duration than recorded 48 hours orlater to was designated a delayed skin response [6,7,19,20,23-25,40,43,61,76-80].

Spirometry

The asthmatic responses were monitored by means of spirometry (Spirograph D-75; Lode NV, Groningen, The Netherlands), recording the FVC and FEV_1 ,and evaluated by the following criteria: (1) the decrease in FEV_1 of less than 10% with respect to the pre- challenge values as negative, from 10% to 20% as doubtful, and of 20% or more as positive asthmatic response; (2) the decrease in FEV_1 within 2 hours after the challenge was considered to be an immediate response (IAR), that occurring between 4 and 24 hours to be a late response (LAR), and response appearing later than 24 hours after the challenge to be a delayed response (DYAR [6,7,19,20,23-25,40,43,61,76-82].

Food used for the ingestion challenge

The quantities of foods used for the food ingestion challenges were similar to those consumed usually by the patients in order to obtain the highest degree of reproducibility (Table 2). The control ingestion challenges were performed with one of the indifferent foods, such as cooked rice, cooked potatoes or 5% glucose solution according to the same schedule as those with the experimental foods [6,7,19,20,23-25,75].

Schedule of the food challenge

The food ingestion challenges as well as the spirometry were performed according to the European and international standard procedures [58,81,82] modified by us [19,23,25,76-79] by the following schedule: (1) recording of the initial (baseline) values at 0, 5 and 10 minutes; (2) ingestion of the food within 10 minutes, followed by a 1-hour waiting interval to allow the food to be ingested. During this interval the parameters were measured four times to exclude an unexpected or too early reaction; (3) recording of the post-challenge values at 0, 5, 10, 20, 30, 45, 60, 90 and 120 minutes, and every hour up to the 12^{th} hour and every second hour duringthe 22^{nd} and 38^{th} hour, the 46^{th} and 58^{th} hour interval [19,23,25,76-79].

Control group

Fifteen patients suffering from perennial bronchial asthma, developing 15 late asthmatic responses (LAR) to BPT with cat or dog danders, however demonstrating negative history, skin test and RAST for the foods, volunteered to participate as controls. In these 15 patients the ingestion challenges with the most frequently consumed food, usually milk, cheese, peanuts, almonds or hazelnuts were performed according to the same schedule as applied in the patients studied.

Protection tests with disodium cromoglycate administered orally

In the 62 patients demonstrating positive asthmatic responses to the food ingestion challenge, the food ingestion challenges were repeated twice, one time after the pre-treatment with oral disodium cromoglycate (DSCG) and other time after pre-treatment with the placebo. The design of the study was double-blind, crossover, placebo-matched. The basic schedule of the protection tests (pre-treated challenge) was similar to that of the non-pretreated challenge. The patients were pretreated with disodium cromoglycate and a placebo in a daily oral dose of 4×200 mg (=4×1 capsule), starting 2 weeks before and continuing throughout the challenge day up to 3 days after the challenge. The test was separated by an interval of 7 days. The protection tests with oral disodium cromoglycate were considered to be clinically significant when the FEV_1 and/or FVC and FEV_1 values recorded after the pretreated food ingestion challenge improved by at least 50% or

more with respect to the values recorded after the non-pretreated food ingestion challenge.

Statistical analysis

Asthmatic responses were analyzed by generalized multivariate analysis of the variance (MANOVA) model [83]. The polynomials were fitted to the mean curves over time (8 time-points within 120 minutes and 14 time-points up to 24 hours after the challenge), and the appropriate hypotheses were tested by the modified MANOVA computerized system.

In every patient the post-challenge FEV_1 values measured at each time-interval were compared with the pre-challenge values and evaluated by Wilcoxon matched-pair signed-rank test. The mean post-challenge FEV_1 values were compared with corresponding post-challenge control values at each of the time-points and analyzed by the Mann-Whitney U test. The results of both the protection tests (disodium cromoglycate and placebo) and their differences were statistically analyzed and evaluated by the Wilcoxon paired-signed-ranks test. A p value<0.05 was considered to be statistically significant.

Results

Types of asthmatic responses

The 62 patients developed 17 isolated immediate asthmatic responses (IAR; p<0.01), 21 isolated late responses (LAR; p<0.001), 8 dual late responses (DLAR, a combination of an immediate and late response; p<0.05), 11 isolated delayed responses (DYAR; p<0.05) and 5 dual delayed asthmatic responses (DDYAR, a combination of an immediate and a delayed response; p<0.05) (Tables 3-5 and Figures 1-5). The time-course of the particular asthmatic response types was as follows: IAR: onset within 80 minutes, maximum within 120 minutes and resolving within 150-180 minutes after the food ingestion; LAR: onset 4-6 hours, maximum 8-12 hours, resolving within 24-26 hours after the food ingestion; DYAR: onset 26-30 hours, maximum 32-38 hours, resolving within 56 hours after the food ingestion in most of the patients [7,19,21,23-25].

In 47 patients of the group I, in whom the food allergy participated as an additional cause, the following asthmatic response types to food ingestion challenge were registered: 14 IAR, 13 LAR, 5 DLAR, 8 DYAR and 3 DDYAR. In 15 patients of the group II, in whom the food allergy was solely cause of the asthmatic complaints, 3 IAR, 8 LAR, 3 DLAR, 3 DYAR and 2 DDYAR were observed.

Control ingestion challenge

No significant changes in the FVC and/or FEV1 values were recorded during the 62 control food ingestion challenges (p>0.1).

Protection tests with oral disodium cromoglycate

The protective effects of oral disodium cromoglycate as compared with the placebo were statistically highly significant for IAR (p<0.001) and LAR (p<0.001), distinctly significant for DLAR (p<0.01) and significant for DYAR (p<0.05) and DDYAR (p<0.05) (Figures 1-5). The distribution of the protective effects of disodium cromoglycate on the particular asthmatic response types was as follows: (1) The IAR was prevented fully in 11 cases (=65%), decreased significantly in 5 cases (=29%) and 1 IAR case (=6%) was not affected; (2) The 14 LAR cases were prevented fully (=67%) and 7 cases were decreased significantly (=33%); (3)All of the 8 DLAR cases were decreased significantly (=100%); (4) The 1 DYAR case was prevented fully (=9%), 9 cases were decreased significantly (=82%) and 1 case was not affected (=9%); (5) The 4 DDYAR cases were decreased significantly (=80%), whereas 1 case remained unaffected (=20%). No differences were observed in the protective effects of oral DSCG with respect to the individual foods (p>0.2).

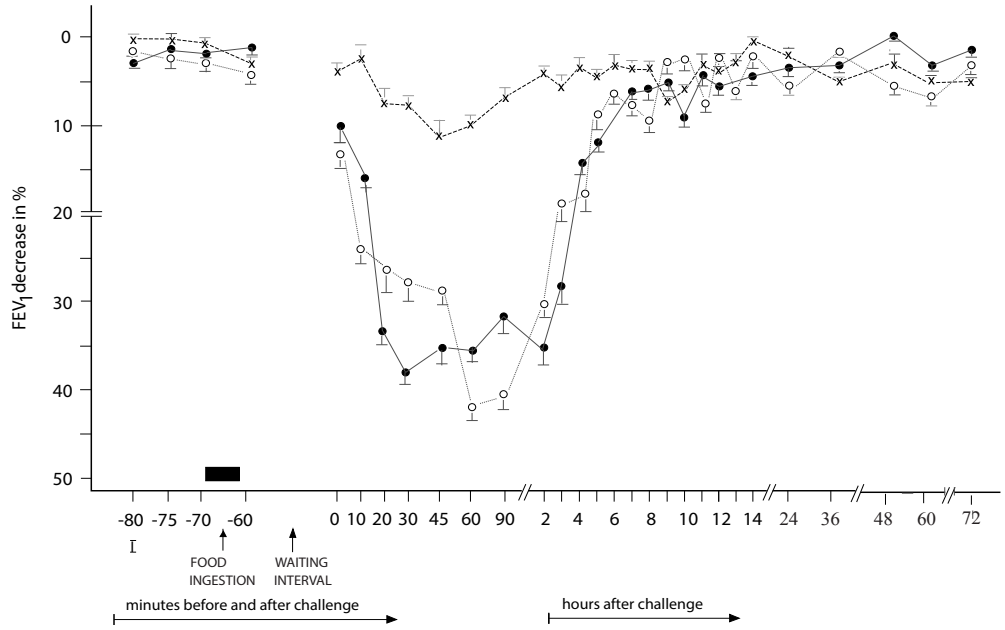

Figure 1: Immediate asthmatic response to the food ingestion challenge (IAR). The mean percentage changes in the FEV_1 values calculated from all patients with positive IAR (n=17).
○=non-pretreated IAR; ●=IAR pretreated with Placebo; x=IAR pretreated with oral DSCG
I=Initial (baseline) values; Waiting interval=1 hour; Bars: means ± SEM

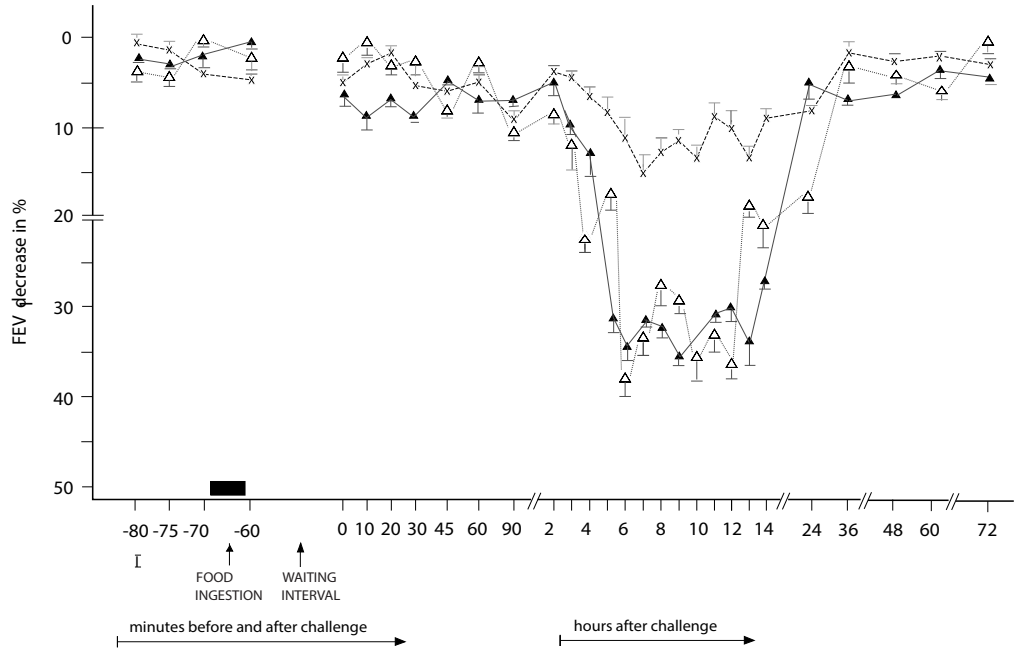

Figure 2: Late asthmatic responses to the food ingestion challenge (LAR). The mean percentage changes in the FEV_1 values calculated from all patients with positive LAR (n=21).
Δ=non-pretreatedLAR; ▲=LAR pretreated with Placebo; x=LAR pretreated with oral DSCG
I=Initial (baseline) values; Waiting interval=1 hour; Bars: means ± SEM

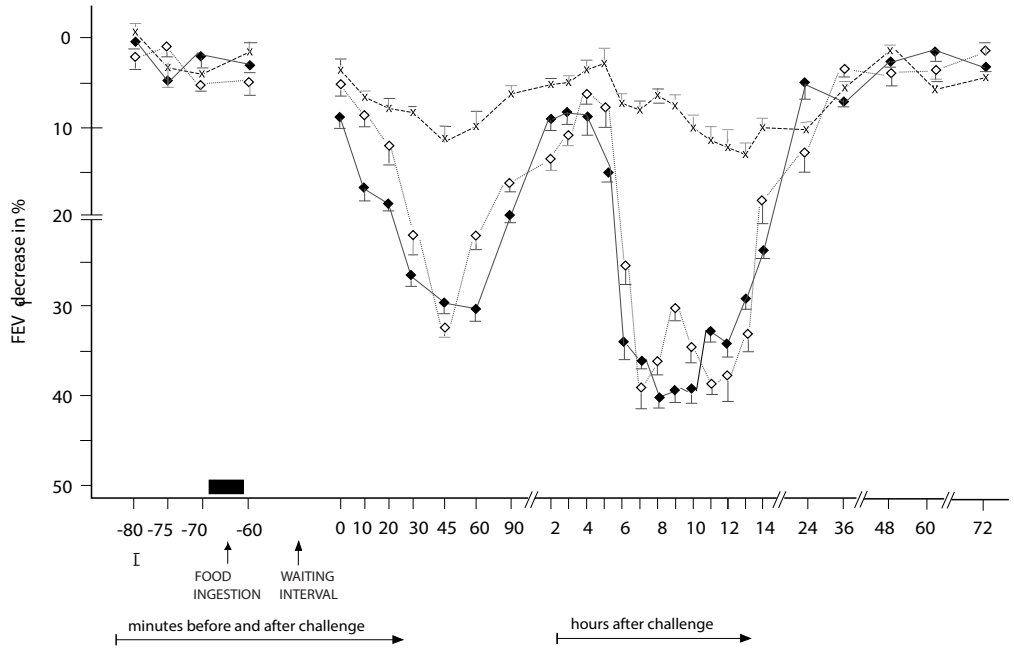

Figure 3: Dual late asthmatic response to the food ingestion challenge (DLAR). The mean percentage changes in the FEV_1 values calculated from all patients with positive DLAR (n=8).
◇=non-pretreated DLAR; ◆=DLAR pretreated with Placebo; x=DLAR pretreated with oral
I=Initial (baseline) values; Waiting interval=1 hour; Bars: means ± SEM

Protection tests with oral placebo

The orally administered placebo did not affect any of the 62 asthmatic responses to food ingestion challenge ($p>0.2$) and it was therefore fully ineffective.

Discussion

The causal involvement of food allergy in patients with bronchial asthma remains still underestimated and poorly understood. The participation of food allergy in bronchial asthma symptoms

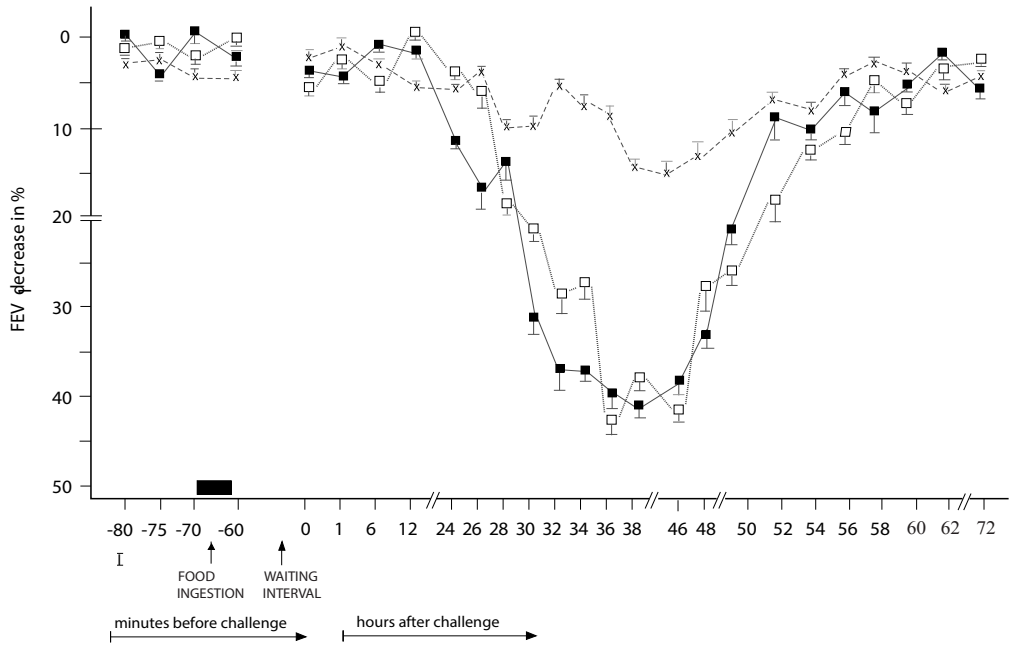

Figure 4: Delayed asthmatic response to food ingestion challenge (DYAR). The mean percentage changes in the FEV_1 values calculated from all patients with positive DYAR (n=11).
□=non-pretreated DYAR; ■=DYAR pretreated with Placebo; x=DYAR pretreated with oral DSCG
I=Initial (baseline) values; Waiting interval=1 hour; Bars: means ± SEM

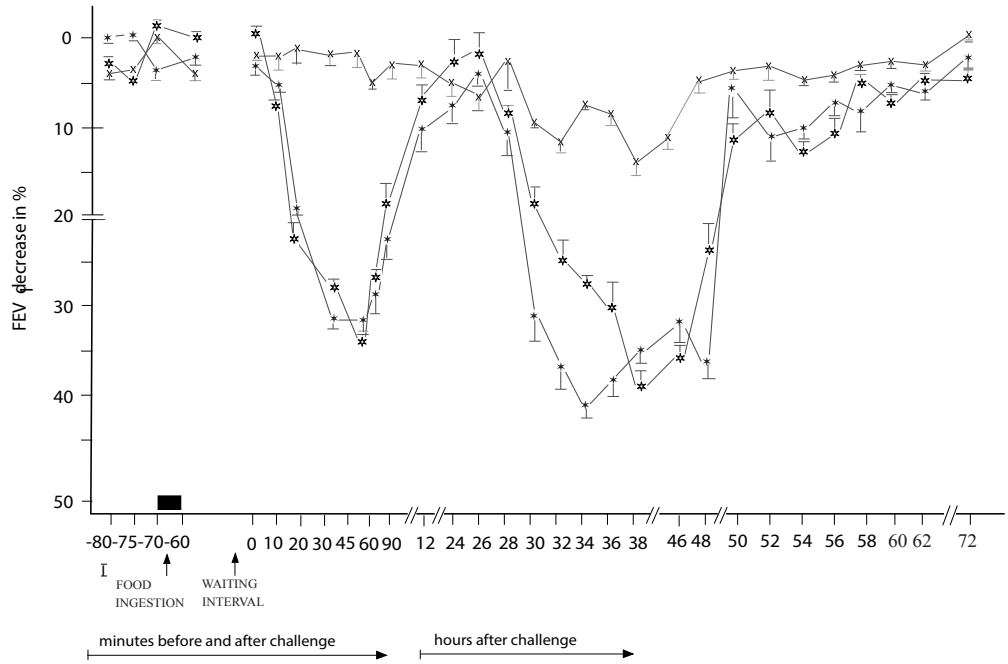

Figure 5: Dual delayed asthmatic response to food ingestion challenge (DDYAR). The means percentage changes in the FEV_1 values calculated from all patients with positive DDYAR (n=5).
✱=non-pretreated DDYAR; ✶=DDYAR pretreated with Placebo; x=DDYAR pretreated with oral DSCG
I = Initial (baseline) values; Waiting interval=1 hour; Bars: means ± SEM

has already been discussed in the literature, sometimes from controversial points of view [1-5,7,12-17,19,21,23-25-27,37-42, 45,48,49,52,53,62,66,68,70,71,84-88]. There is still a dearth of information concerning the well-documented data conforming the causative role of foods and food allergy in asthmatic complaints. The diagnostic confirmation of the role of foods and food allergy in the clinical manifestations is performed in the practice by means of disease history, skin tests and/or determination of the food-specific IgE antibody in the serum. However, these tests demonstrate variable degree of correlation with the clinical manifestation of bronchial asthma and their predictor

value does not seem to be fully satisfactory [1-8,11,12,14,15,19-21,23-25,27,28,31,38-39,41,45,48-53,55-57,60,61,80,81]. The involvement of the food allergy in in the bronchial asthma, can only be confirmed by means of the food ingestion challenge, demonstrating particular types of asthmatic response induced by certain food(s), which can be recorded quantitatively by means of objective functional parameters, such as lung function , in their dynamic course [2,7,8,10,11,14,15,19, 21,23-25,38,39,40,44-51,53-61,63, 64,84-88].

The five types of asthmatic response induced by food ingestion challenge in bronchial asthma patients, described in this as well as in our previous papers [7,19,23-25,84], may be comparable with the basic types of the asthmatic response to the bronchial challenge with inhalant allergens [76-79].

The exact hypersensitivity mechanisms underlying the particular types of asthmatic response to food ingestion challenge are not yet fully clarified and need more concurrent immunologic and clinical studies. The IAR due to the IgE-mediated food allergy has been most extensively investigated [1-3.5.7-12,14-17,21-23,25,27,37,38,40,41,45,53,67]. The LAR to food allergy has also been reported, however, the underlying immunologic mechanism has not been satisfactorily clarified [7,16,19,21,23,26-28,37,66,89,90]. Some investigators suggested a possible participation of immune-complexes, whereas others presumed involvement of IgE antibodies and/or various modifications of the IgE-mediated hypersensitivity mechanisms. In the DYAR to food ingestion challenge, described already by usin the past [7,19,23,84], which is analogical to the DYAR induced by inhalant allergens [78,79] the involvement of the cell-mediated hypersensitivity mechanism(s) could be presumed. Nevertheless, there is still a great dearth of structural information and research data concerning the exact role and the mode of involvement of immunological mechanisms in the particular types of the food-induced asthmatic response in large group of well-defined and diagnosed patients with bronchial asthma. The protective effects of oral disodium cromoglycate on various clinical manifestations due to the adverse reactions to foods, among which to food allergy, have regularly been studied and reported in the literature [1-7,15,24,65,67-74]. However, in most of these studies, the protective effects of this drug on the skin disorders, such as atopic eczema, dermatitis, urticaria, colon disorders, such as colitis ulcerosa, Crohn's disease, oesophagitis or multiple symptoms due to the adverse reactions to foods have been investigated. Moreover, in most of these studies, the protective effects of disodium cromoglycate were evaluated predominantly by recording of subjective parameters, such as symptom scores. Unfortunately, the protective effects of disodium cromoglycate were not related to the qualitatively and quantitatively well-defined stimulus, such as ingestion challenge with a certain food(s). Nevertheless, data illustrating the possible protective effects of oral disodium cromoglycate on the asthmatic response types induced by food allergy, in a large group of well-defined patients with bronchial asthma, are not available until yet.

Disodium cromoglycate (Cromolyn, DSCG) is a disodium salt of 1, 3-bis-(2-carboxychromone-5-yloxy)-2-hydroxypropane. Disodium cromoglycate administered orally in a daily dose of 4×200 mg has demonstrated statistically significant protective effects on all 5 types of asthmatic response to food ingestion challenge, however, with some differences and variations [91-95]. The differences in the protective effects of the oral DSCG could partly be explained by the manifold pharmacologic and biochemical effects of this drug, which can be summarized as follows: (1) Protection of mast cells and basophils from their degranulation and subsequent release of various mediators and constituents; (2) Stabilization of the cell membranes by blocking calcium transport, inhibition of calcium gate openings induced by antigen and) Elevation of the membrane-associated cyclic adenosine monophosphate (cAMP); (3) Inhibition and decrease of the neutrophil mobility and chemotactic activity; (4) Increase of the cAMP and decrease cGMP in neutrophils, thrombocytes and lung tissue cells; (5) Inhibition of action of protein kinase C , an enzyme that requires calcium phosphatidylserine for the full expression of its activity; (6) Reduction of a number of complement reactions, such as C3b and immunoglobulin G (IgG) rosettes (Fcγ) on human eosinophils; (7) Inhibition of TNFα release from human lung , intestinal and peritoneal mast cells; (8) Inhibition of production of TNF-α and IL-5 by human lung specimens; (9) Inhibition ofIgE-dependent enzyme production and release of neutrophil chemotactic factor from human alveolar macrophages; (10) Reduction of numbers of human eosinophils, neutrophils, T-lymphocytes and tissue macrophages; (11) Decrease of the expression of ICAM-1, VCAM-1 and ELAM-1 of in biopsies of the bronchial mucosa and on the epithelial cells; (12) Inhibition of the influx of neutrophils and release of TNFα and IL-6 into BAL fluid following allergen challenge; (13) Inhibition of release of prostaglandin D_2 and leukotriene C_4 from dispersed lung cell and suppression of leukotriene C_4 synthesis by inhibition of mRNA expression of LTC_4 synthase; (14) Suppression of antibody-dependent cytotoxicity of human neutrophils and eosinophils, and the anti-IgG_4–induced degranulation of human basophils; (15) Increase the survival time of human platelets and reduction the IgE-dependent monoamine uptake in platelets; (16) Inhibition of IgE isotype switching and enhancement of IgG_4 production; (17) Inhibition of cell adhesion and immigration of neutrophils, their recruitment onto vascular endothelium via Annexin-A1 mobilization, as well as the myeloperoxidase release from these cells; (18) Decrease of production of eosinophilic cationic protein; (19) Decrease of amounts of leukotriene B_4 and C_4 in blood, BAL fluid and tears; (20) Inhibition of plasma extravasation and airway neurogenic inflammation, presumably through functional antagonism of tachykinins; (21) Inhibition of assembly of an active NADPH oxidas (nicotinamide adenine dinucleotide phosphate or triphosphopyridine nucleotide) in neutrophils and prevention of oxygen radical-induced tissue damage; (22) Prevention of the G-protein activation; (23) Inhibition of protein kinase C (PKC) activity; (24) Inhibition of proliferative responses of T- and B-cell subsets stimulated with mitogens together with recombinant IL-2(rIL-2); (25) Inhibition of absorption of the major soybean allergen, Gly m Bd30K in human intestinal Caco-2 cells via clathrin- and/or caveolae-dependent endocytosis.

On the other hand, there is a lack of structural knowledge of the processes in the gastro-intestinal tract through which the foods and their parts act as an antigen and initiate the hypersensitivity reactions leading to the certain type of response of the certain organ [3,5-9,13,16,17,19-37,80]. The most important questions of this poorly understood area of clinical allergology concern the role of the intestine in controlling and monitoring the uptake of ingested foods and their antigens, the mechanisms involved directly as well as indirectly during the resorption of the potential antigens, presentation of the food antigens and their components by which types of APC cells to which kinds of target cells, which type of cells are activated and involved in the further steps of this immunologic process, the mode of antigen transport from the gut to other organs and tissues, e.g. bronchial tree and lastly the whole complex of factors determining the target and response-organ as well as the type of the organ response [3,5-9,13,16,17,19-37,80].

There are several hypotheses attempting to explain the the

mechanisms through which the foods participate in hypersensitivity states. One of the most interesting and promising theories concerns the mucosal barrier and its role in handling of (food) antigen by the gut (gastro-intestinal tract) [6,7-9,19,21,22,28-37]. The involvement of the particular hypersensitivity mechanisms in the individual types of the organ response, e.g. asthmatic response, to ingested food is not yet fully clarified. However, there is evidence that besides the type I (immediate) hypersensitivity, also the type III (late, immune-complex-mediated) and the type IV (delayed, cell-mediated) hypersensitivity may be involved in the pathogenesis of the food allergy [1-9,16,19-36,59].

Regarding the results of this study, of our previous studies [7,19,23,25,84] and the other investigators results [9,13,21,22,26-35] the involvement of the immediate hypersensitivity mechanism (Type I) in the IAR, the late hypersensitivity mechanisms (Type III) in the LAR and the delayed hypersensitivity (cell-mediated, Type IV) in the DYAR to the food ingested, at least in some of their modifications, cannot be excluded in the patients with bronchial asthma demonstrating positive asthmatic responses to food ingested. Despite a dearth of exact knowledge of the (hypersensitivity) mechanisms underlying the basic types of asthmatic response to foods ingested as well as the exact mode of pharmacologic action of oral DSCG, it can be concluded, that the disodium cromoglycate in a daily oral dose of 4×200 mg significantly prevented all 5 basic types of asthmatic response to food ingestion challenge. Oral DSCG seems therefore to be a suitable drug for the prophylaxis and control of asthmatic complaints due to the ingested foods acting most probably through the food allergy mechanism(s). If necessary, the oral DSCG can be combined with other additional pharmacologic agents to improve the control of asthmatic complaints.

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