

26. Rognum TO, Fausa O, Brandtzaeg P. Immunohistochemical evaluation of carcinoembryonic antigen, secretory component, and epithelial IgA in tubular and villous large bowel adenomas with different grades of dysplasia. *Scand J Gastroenterol* 1982;17:341-8.
27. Badr EL, Din S, Trejdosiewicz LK, Heatley RV, Losowsky MS. Local immunity in ulcerative colitis: evidence for defective secretory IgA production. *Gut* 1988;29(8):1070-5.
28. Henzen Logmans SC, Schipper NW, Poels LG, Stolk K, Kenemans P. Use of statistical evaluation of antigen profiles in differential diagnosis between colonic and ovarian adenocarcinomas. *J Clin Pathology* 1988;41(6):644-9.
29. Harris JP, South MA. Secretory component: a glandular epithelial cell marker. *Am J Pathol* 1981;105:47-53.

An examination of food hypersensitivity as a cause of increased bronchial responsiveness to inhaled methacholine

John F. Zwetchkenbaum, MD, Roberta Skufca, BA, and
Harold S. Nelson, MD *Providence, RI, and Denver, Colo.*

To determine if food challenges could alter bronchial hyperresponsiveness, methacholine challenges were performed before and 24 hours after double-blind, placebo-controlled food challenges on 11 subjects with asthma with a history of food-induced asthma and positive skin prick tests to the suspect food. An equal number of patients demonstrated increased methacholine sensitivity after food and placebo challenges. Thus, we could not find evidence that allergic reactions to food induced bronchial hyperresponsiveness. (J ALLERGY CLIN IMMUNOL 1991;88:360-4.)

Key words: Food hypersensitivity, methacholine, bronchial responsiveness

Asthma as an adverse food reaction, whether it is immunologic or nonimmunologic, has been confirmed by DBPCFCs in only 0% to 5.2% of patients who presented with a history of food-induced respiratory symptoms.¹⁻⁴ Despite the prevalent view that food plays a minor role in respiratory allergy, many patients report that food can induce symptoms of asthma. The inability to confirm these reports may reflect the limitations of the doses achievable in the blind challenge¹ or the absence of other variables whose combined presence leads to symptoms,⁵ such as the added stress of exercise⁶ or concomitant exposure to seasonal pollens.

Abbreviations used

DBPCFC: Double-blind, placebo-controlled food challenge
PEFR: Peak expiratory flow rate
PC₂₀: Provocative challenge producing at least 20% drop in FEV₁

It has been hypothesized that allergy to food may contribute to respiratory symptoms by increasing bronchial hyperresponsiveness.^{3,7} This effect of food could be enough to reduce the threshold for bronchial airway constriction when the patient is subsequently exposed to other allergenic or nonallergenic stimuli, whereas the food by itself may not worsen pulmonary function after ingestion of conventional quantities.

Increased bronchial hyperresponsiveness has been reported after inhalant allergen challenge in patients with asthma with documented IgE sensitivity to the allergen. We performed methacholine challenges after DBPCFCs in 11 subjects with asthma with a history of food-induced asthma and positive SPTs to the sus-

From the National Jewish Center for Immunology and Respiratory Medicine, Denver, Colo.

Received for publication July 5, 1990.

Revised April 18, 1991.

Accepted for publication April 18, 1991.

Reprint requests: Harold S. Nelson, MD, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Denver, CO 80206.

1/1/30310

pect food to determine if food challenges could also affect methacholine sensitivity. If an increase in bronchial responsiveness occurred, it might indicate that this more sensitive challenge procedure was required for select patients and that foods may play a significant role in respiratory allergy.

METHODS

Subjects

Patients were selected on the basis of a strong history for recurrent episodes of food-induced lower respiratory symptoms (wheezing, dyspnea, chest tightness, and cough) (see Table II). All patients had an (3 mm or larger wheal⁸) SPT to the incriminated food. Subjects with a history of life-threatening reaction with prior ingestion of specific food were not challenged with that particular food. They were accepted for challenge if there was another food to which they had a history of a respiratory reaction and were SPT positive but had no history of a previous life-threatening reaction.

Exclusion criteria included any patient with a history of significant cardiovascular disorder, emphysema, chronic bronchitis, respiratory infection within the previous 6 weeks, or was a current smoker. Also excluded were any patients whose baseline FEV₁ while they were receiving long-term asthmatic medication was <70% predicted at initial evaluation before challenge, any patient receiving oral or inhaled corticosteroids, and any patient with marked methacholine sensitivity (PC₂₀, 0.31 mg/ml or weaker concentration).

More than 100 patients answered our advertisement. Of that number, 34 patients with strongly suggestive histories were screened in the clinic. Eleven subjects (six male and five female subjects) between 20 and 53 years of age (mean age, 38.1) met the criteria for study. Seventeen patients were rejected because their SPTs did not support their history. Other reasons for rejection included methacholine reactivity at 0.31 mg/ml, corticosteroids (two patients), and inability to demonstrate methacholine reactivity at 25 mg/ml (one patient).

All patients had a complete physical examination, including baseline spirometry. Patients older than 40 years of age had an electrocardiogram performed to rule out unsuspected cardiac disease that might place the patient at risk during the food and methacholine challenge.

Skin testing

SPTs were performed on the back with a panel of 16 foods commonly found in the diet plus foods not in the panel but suspected by the patient of producing respiratory symptoms. PSTs were performed with 1:20 (wt/vol) glycerinated extracts (Hollister-Stier Laboratories, Spokane, Wash.) or with fresh food. With this technique, either the food pulp was pierced with the skin test needle followed by prick with the needle, or a drop of extracted juice was placed on the back and pricked. Histamine phosphate (1 mg/ml of histamine base) and 50% glycerol-saline were used as positive and negative controls. A positive reaction was a wheal 3 mm diameter or larger at 15 minutes with a

negative glycerol-saline control.⁸ Subjects refrained from taking H₁ antagonists or tricyclic antidepressants at least 72 hours before skin testing. Astemizole was withheld for at least 6 weeks.

Study design

The study was of double-blind, placebo-controlled, two-period crossover design. Patients were randomly assigned to one of two sequences: test food followed by placebo or placebo followed by food.

The food, which by history and skin tests exhibited the largest reaction, was tested. Those subjects who had not previously eliminated the suspect food from their diet had a 2-week elimination diet before the DBPCFC. Methacholine challenges were performed at presentation and after the 2-week elimination diet for comparison. Food products were obtained in powdered form from commercial sources. Nuts were blended fresh to powdered form. Food powder was placed in opaque capsules. Dextrose or sucrose was used as placebo and placed in identical capsules.

Bronchial methacholine testing

The methacholine challenge was not performed if the patient's FEV₁ was <60% predicted. The challenge was performed according to the guidelines of Chai et al.⁹ The solutions used were saline and 0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5.0, 10.0, and 25.0 mg/ml of methacholine; 1 ml of each dilution was serially added to a DeVilbiss 646 (DeVilbiss Co., Somerset, Pa.) nebulizer and nebulized with a Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, Md.) powered by an oxygen tank with a pressure of 20 psi. All dilutions of methacholine were made fresh at least every 2 weeks. Five inhalations of each dilution were made from functional reserve capacity to total lung capacity. FEV₁ and FVC were measured 90 seconds after each dose. Spirometry was repeated after another 90 seconds to document persistence of the drop in FEV₁ before accepting it as a positive response. The testing was concluded when the FEV₁ decreased by 20% or more of baseline after saline ("positive" response, PC₂₀) or after the 25 mg/ml dose had been administered. All patients with a 20% or more decrease in FEV₁ were treated with two inhalations of albuterol, metered-dose inhaler, to prevent the compromise of their pulmonary status before the food challenge. Medications were withheld according to criteria used in the Pulmonary Physiology Unit of National Jewish Center for Immunology and Respiratory Medicine: inhaled bronchodilators, 4 to 6 hours; inhaled atropine, 12 hours; cromolyn sodium, 8 hours; and oral bronchodilators, 8 hours. Oral theophylline was not withheld.

Food challenges (protocol) (Table I)

The challenges were performed in an area in which medical supervision was maintained and resuscitation equipment was available. At least a 7-day washout period between the challenges was provided to prevent crossover effect between the challenges.

Baseline FEV₁ and FVC (Eagle II spirometer, Warren Collins Inc., Braintree, Mass.) and PEF_R (mini-Wright peak

TABLE I. Protocol

Visit No. 1: Baseline evaluation
History and physical examination, including spirometry
Skin prick testing
If an acceptable candidate:
Baseline methacholine challenge
Begin 2-week elimination diet in patients who had not avoided the test food
Visit No. 2:
Methacholine challenge
Progressive food or placebo challenge
Visit No. 3: (24 hr)
Methacholine challenge
Visit No. 4: (7 or more days later)
Methacholine challenge (same time of day as visit No. 2)
Progressive food or placebo challenge
Visit No. 5: (24 hr)
Methacholine challenge

flow meter, Armstrong Medical Industries, Inc., Northbrook, Ill.) were obtained. This procedure was followed by the methacholine challenge. Ten minutes after completing the methacholine challenge, the patient received one tenth (1000 mg) of the total challenge dose of placebo or test food. Thirty minutes after completing the methacholine challenge, vital signs, FEV₁, PEFR, and overall clinical status were assessed. If the above parameters were stable (<20% change in FEV₁; heart rate, >50 and <120; systolic blood pressure, >90 and <180), three tenths (3000 to 4000 mg) of the total challenge dose was administered. One hour after completing the methacholine challenge, vital signs, FEV₁, PEFR, and overall clinical status were again assessed. If the patient was stable as described above, the final six tenths of the challenge dose to produce a total of approximately 10 to 11 gm of placebo or test food was administered. If at any time the parameters indicated that the patient was unstable, patients received bronchodilator treatment (albuterol by nebulization), and no additional challenges were performed that day; however, the methacholine challenge was performed on day 2 as scheduled.

Two hours after the initial methacholine challenges, the patients were discharged from the research unit only if their PEFR and FEV₁ had returned to baseline and vital signs and overall clinical status were stable. The patients maintained hourly PEFR measurements and symptom diaries for the next 5 hours and thereafter if symptoms occurred. The patients were allowed to resume their long-term asthma medications but withheld them before the second methacholine challenge on day 2 according to the schedule listed above. The methacholine challenge on day 2 was performed at approximately the same time of day as on day 1.

Statistical analysis

A sample size of 10 was calculated to provide a >70% chance of detecting a treatment difference, should it exist, with a one-tailed, Student's paired *t* test at the 0.05 level, assuming the mean difference equaled the standard deviation of the differences, in this case, at least on dilution. The principle response was PC₂₀ measured at time 0 and 24 hours. A decrease in PC₂₀ to at least onefold weaker concentration after food challenge compared to the change after placebo challenge was considered a significant response.

RESULTS (Table III)

Patient No. 7 was the only patient who developed an early asthmatic response to food challenge. This response occurred roughly 2 hours after the albuterol inhalation treatment administered at the completion of the methacholine challenge. Five minutes after ingesting the second food dose (3000 mg), he developed gastrointestinal upset and became lightheaded, followed by watery diarrhea. His FEV₁ was 102% predicted. After 30 minutes, his FEV₁ had decreased to 75% predicted and later <50% predicted, despite treatment. No additional challenges were administered. Diarrhea persisted through the night, but his respiratory symptoms abated with only mild worsening of PEFR.

Patient No. 1 complained of mild chest tightness during the 5 hours after the food challenge, which was not noted after placebo challenge. His PEFR was unchanged.

Patient No. 3 noted symptoms of shortness of breath and more severe cough without a change in PEFR the evening of her food challenge. These symptoms were not noted after the placebo challenge.

Patient No. 8 did not complain of respiratory symptoms or have a change in PEFR the evening of his food challenge but did note symptoms of sore throat, dizziness, and pruritus that evening that was not noted during the placebo challenge.

Finally, *Patient No. 9* noted mild symptoms of wheezing, cough, and chest tightness with an 8% to 10% decrease in PEFR during the 5 hours after food challenge that was not noted with placebo challenge.

All patients except patient No. 7 tolerated the food challenge to the total dose of 10 to 11 gm. Patients Nos. 1, 3, and 8 had significant increases in methacholine sensitivity after food compared to after placebo challenge. Patients Nos. 7, 9, 10, and 11 had significant increases in methacholine sensitivity after placebo compared to after food challenge. Patient No. 10 had hoed a garden before performing the final methacholine challenge on day 2 of challenge No. 2

TABLE II. Clinical histories of study patients

Pt	Age (yr)	Sex	Food-related complaint	Food tested	SPT	SP
1	44	M	Asthma	Brewer's yeast	+	+
2	24	M	Asthma	Tomato	+	+
3	51	F	Asthma	Milk	+	+
4	36	F	Asthma, urticaria, vomiting	Milk	+	+
5	44	F	Asthma	Mushroom	+	+
6	25	M	Asthma, lightheaded	Pea	+	—
7	53	M	Asthma, GI distress, lip swelling	Egg	+	+
8	51	M	Asthma, pruritus (AD)	Fish	+	+
9	29	F	Asthma, urticaria	Pecan	+	+
10	29	M	Asthma, pruritus (AD)	Soy	+	+
11	33	F	Asthma	Peanut	+	+

Pt, Patient; AD, atopic dermatitis; GI, gastrointestinal; +, positive, wheal 3 by 3 mm; —, negative, wheal <3 by 3 mm; SP, sensitive to seasonal pollen.

(placebo). His baseline spirometry that day was significantly reduced (26% decrease compared to day 1).

DISCUSSION

In this study there was an increase in methacholine sensitivity by one or more dilutions in three patients after food challenge and four patients after placebo challenge. Patient No. 10, who was known to have significant exercise-induced asthma, hoed a garden just before his final methacholine challenge on day 2 of challenge No. 2 (placebo). He was symptomatic at presentation. His significant increase in methacholine sensitivity is therefore discounted. Given the equal number with altered responsiveness after both food and placebo challenges, we cannot attribute the apparent increases in methacholine sensitivity that occurred after the three food challenges to food hypersensitivity.

Only one patient (No. 7) clinically demonstrated worsening pulmonary function after food challenge. Interestingly, his methacholine sensitivity increased more after placebo than after food challenge. Of the four patients with lower respiratory symptoms after food challenge, two developed a greater increase in methacholine sensitivity after food and two patients after placebo. In addition, the three of 11 patients who had not maintained strict food avoidance of the implicated food before the study and thus had a 2-week elimination diet did not demonstrate improved methacholine sensitivity after the 2-week elimination diet. These factors rule against a role for foods in inducing bronchial hyperresponsiveness.

For the reasons cited previously, it is unlikely that the increase in methacholine sensitivity after food

TABLE III. Provocative challenge findings

Pt	Challenge	Active/placebo	PC ₂₀ dose (mg/ml)	
			Day 1	Day 2
1	1	P	5.0	5.0
	2	A	2.5	0.31
2	1	A	0.62	1.25
	2	P	2.5	2.5
3	1	A	5.0	0.31
	2	P	0.62	0.31
4*	1	P	>25	>25
	2	A	>25	>25
5	1	A	0.62	0.15
	2	P	0.62	0.15
6	1	A	1.25	1.25
	2	P	10.0	>25
7	1	P	1.25	0.31
	2	A	0.62	0.31
8	1	A	2.5	1.25
	2	P	0.62	1.25
9	1	P	5.0	1.25
	2	A	0.62	0.62
10	1	A	0.62	0.62
	2	P	1.25	0.15
11	1	A	>25	>25
	2	P	>25	5.0

Pt, Patient; A, active; P, placebo.
*PC₂₀ at initial evaluation, 5.0 mg/ml.

challenge in patients Nos. 1, 2, and 8 represents the effect of food hypersensitivity.

Our results differ from results of Wilson et al.⁷ who demonstrated a significant change in histamine reac-

tivity after cola drinks in six of 10 children tested. Although the mechanism for the cola drink-induced increase in airway responsiveness to histamine was not investigated, it appears to be nonimmunogenic. Onorato et al.,⁴ using DBPCFC, was able to elicit symptoms of atopic dermatitis in one patient after a cola beverage challenge but could not prove IgE sensitivity. All of our patients had evidence for IgE sensitivity to the food in question. Unlike the study of Wilson et al.⁷ in which histamine challenges were performed 30 minutes after food challenge, our methacholine challenges were performed at 24 hours. We chose 24 hours to perform the repeat methacholine challenge because it obviated any concern about diurnal variation in bronchial reactivity or the protective effect of albuterol treatment used to reverse the decrease in FEV₁ caused by the baseline methacholine challenge. It also corresponded to our patients' common complaint of worsening respiratory symptoms 24 to 48 hours after food ingestion. Bronchial hyperresponsiveness after inhalant allergen challenge has been demonstrated beyond 48 hours.¹⁰

In conclusion, this study could not demonstrate increased methacholine sensitivity after food challenge compared to after placebo challenge in a group of patients with asthma with a history of food-induced asthma and documented IgE sensitivity to the food. Despite the occurrence of a significant increase in methacholine sensitivity after food challenge in three patients, an equal number of patients demonstrated an increase in methacholine sensitivity after placebo challenge. Therefore, with the use of methacholine challenge, a more sensitive method than spirometry

or peak flow measurements of testing for food-induced respiratory complaints, this study supports previous data that consigned to food a minor role in bronchial asthma in adults.

We thank Victoria Melton for her assistance.

REFERENCES

1. Bousquet J, Michel FB. Food allergy and asthma. *Ann Allergy* 1988;61(2):70-4.
2. May CD. Objective clinical and laboratory studies of immediate hypersensitivity reactions to foods in asthmatic children. *J ALLERGY CLIN IMMUNOL* 1976;58:500-15.
3. Novembre E, de Martino M, Vierucci A. Foods and respiratory allergy [Symposium]. *J ALLERGY CLIN IMMUNOL* 1988;81:1059-65.
4. Onorato J, Merland N, Terral C, et al. Placebo-controlled double-blind food challenge in asthma. *J ALLERGY CLIN IMMUNOL* 1986;78:1139-46.
5. Wilson NM. Bronchial hyperreactivity in food and drink intolerance. *Ann Allergy* 1988;61(2):75-9.
6. Kidd JM III, Cohen SH, Sosman AJ, Fink JN. Food-dependent exercise-induced anaphylaxis. *J ALLERGY CLIN IMMUNOL* 1983;71:407-11.
7. Wilson N, Vickers H, Taylor G, Silverman M. Objective test for food sensitivity in asthmatic children: increased bronchial reactivity after cola drinks. *Br Med J* 1982;284:1226-8.
8. Bock SA, Buckley J, Holst A, May CD. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Allergy* 1977;7:375-83.
9. Chai H, Farr RS, Froehlich LA, et al. Standardization of bronchial inhalation challenge procedures. *J ALLERGY CLIN IMMUNOL* 1975;56:323-7.
10. Durham SR, Craddock CF, Cookson WO, Benson MK. Increases in airway responsiveness to histamine precede allergen-induced late asthmatic responses. *J ALLERGY CLIN IMMUNOL* 1988;82:764-70.