

Food-Dependent Exercise-Induced Anaphylaxis: Possible Impact of Increased Basophil Histamine Releasability in Hyperosmolar Conditions

W Barg, A Wolanczyk-Medrala, A Obojski, K Wytrychowski, B Panaszek, W Medrala

Department of Internal Medicine and Allergology, Wroclaw Medical University, Wroclaw, Poland

■ Abstract

We present a case of anaphylactic shock induced by exercise following celery ingestion. The possible mechanism of food-dependent exercise-induced anaphylaxis (FDEIA) and the laboratory tests for its diagnosis are discussed. We evaluated spontaneous, celery-allergen-induced, and anti-FcεRI-antibody-induced histamine release from basophils obtained from the patient, 2 celery-allergic controls, and 3 healthy controls. Buffers of increasing osmolarity were used to mimic conditions of vigorous physical exercise. Only the patient's basophils showed an increase in spontaneous, anti-FcεRI antibody-induced and allergen-induced histamine release under physiological conditions and with slightly increased medium osmolarity. To our knowledge, this is the first report on the possible role of increased histamine releasability in the pathogenic mechanism of FDEIA. We suggest that FDEIA results from increased histamine releasability triggered by physical effort after exposure to a sensitizing food allergen.

Key words: Food-dependent exercise-induced anaphylaxis. Histamine release.

■ Resumen

Presentamos un caso de shock anafiláctico inducido por el ejercicio, después de la ingestión de apio. Estudiaremos los posibles mecanismos de la anafilaxia inducida por el ejercicio dependiente de los alimentos (AIEDA) y las pruebas de laboratorio para su diagnóstico. Examinamos la liberación de histamina espontánea inducida por anticuerpos anti-FcεRI que provocan los alérgenos al apio, en los basófilos obtenidos del paciente, de 2 controles alérgicos al apio y de 3 controles sanos. Se utilizó un tampón de osmolaridad creciente para simular las condiciones del ejercicio físico enérgico. Sólo los basófilos del paciente mostraron un aumento de la liberación de histamina espontánea dependiente del anticuerpo anti-FcεRI y dependiente del alérgeno, bajo condiciones fisiológicas y con una osmolaridad media levemente aumentada. Hasta donde alcanza nuestro conocimiento, este es el primer registro sobre el posible papel de la liberación de histamina aumentada individualmente, en el mecanismo patogénico de la AIEDA. Por lo tanto, sugerimos que la AIEDA resulta de la liberación de histamina aumentada, desencadenada por el esfuerzo físico después de la exposición a un alérgeno alimentario sensibilizador.

Palabras clave: Anafilaxia inducida por el ejercicio dependiente de los alimentos. Liberación de histamina.

Introduction

The mechanism of food-dependent exercise-induced anaphylaxis (FDEIA), first described in 1979 by Maulitz et al, remains unknown [1]. Its prevalence is not well documented, although it is considered an infrequent phenomenon (found in only 0.017% individuals from a population of 76 000 young Japanese high-school students [2]). We describe a case of anaphylactic shock induced by exercise following celery

ingestion and discuss possible mechanisms of FDEIA and laboratory tests that might be useful for diagnosis.

Case Description

A 22-year-old woman with bronchial asthma and pollinosis experienced collapse, severe hypotension, dyspnea with wheezing, abdominal pain, nausea, hand numbness,

angioedema, urticaria, and generalized pruritus. The event took place while she was playing ball 1 hour after ingesting fresh celery. She recovered after routine treatment with adrenaline, corticosteroids, and phenazoline. The patient had previously been diagnosed with asthma and seasonal allergic rhinitis, and was on regular inhaled treatment (long-acting β_2 -agonists, corticosteroids, chromones) and oral treatment (montelukast and cetirizine). Skin prick tests were positive to mugwort pollens and house dust mites, but she never underwent specific immunotherapy. One year previously, she attended the emergency room due to angioedema of the upper airway with no systemic symptoms. The event took place during a wedding party, but the trigger was not identified.

The patient's allergologic status was evaluated a few months after the anaphylactic shock and a skin prick test for celery was positive. In contrast, the specific immunoglobulin (Ig) E test (both Allergopharma, Reinbek, Germany) was negative. An exercise test was performed, but it induced neither symptoms of anaphylaxis nor significant spirometric findings. Because of the life-threatening anaphylactic reaction, an exercise challenge after celery ingestion was not performed.

We compared histamine releasability from basophils obtained from the patient with that of 3 healthy controls and that of 2 celery-allergic patients who tolerated exercise. It is known that increased medium osmolarity increases both IgE-dependent and IgE-independent histamine releasability from basophils [3,4]. It is also known that increased osmolarity due to intensive physical effort results in amplified release of mediators of allergic reactions [5]. Thus, the histamine release tests were performed using a range of buffers with increasing osmolarity—280 mOsm, 340 mOsm, and 450 mOsm—to mimic conditions of vigorous physical exercise. Increased osmolarity was achieved by the addition of mannitol. The venous blood specimens were collected on EDTA and mixed with dextran solution in the proportion 4:1 (Bühlmann Laboratories AG, Schönenbuch, Switzerland). After 90 minutes of sedimentation at room temperature, the upper phase was transferred into a second tube and centrifuged for 15 minutes at 130g at room temperature. After the supernatant was discarded, cells were suspended at a concentration of

1×10^7 /mL of the stimulation buffer (Bühlmann Laboratories AG). Histamine release was induced by celery allergen at a final concentration of 20 ng/mL, and by anti-Fc ϵ RI monoclonal antibody (both from Bühlmann Laboratories AG). In order to determine spontaneous histamine release (SHR), blood cells were incubated only in stimulation buffer (Bühlmann Laboratories AG). After 40 minutes of incubation at 37°C, the samples were centrifuged at 4°C at 1000g for 3 minutes and the supernatants were tested for histamine concentration. Total histamine content was determined in separate tubes after incubation in Triton X100. The histamine concentration in the samples was determined by Histamine-ELISA (IBL, Hamburg, Germany). All measurements were made in duplicate and the values averaged. The results in the cell samples stimulated with celery allergen and anti-Fc ϵ RI monoclonal antibody are expressed in percentages after subtraction of the SHR values. The positivity cutoff was set at 5%.

In the healthy controls, SHR at physiological osmolarity (280 mOsm) was very low (mean, 2.2%). The increase in medium osmolarity to 340 mOsm and 450 mOsm did not markedly change the SHR values. In the celery-allergic controls, SHR remained at the same low level at physiological osmolarity and at 340 mOsm, and increased to 8.2% at the highest medium osmolarity. However, the patient's basophils exhibited a much higher SHR at physiological osmolarity (9.6%). Increasing medium osmolarity produced an increase in SHR to 15% at 340 mOsm. This remained high at 450 mOsm. Similar differences were observed when the basophils were stimulated by anti-Fc ϵ RI monoclonal antibody. The patient's basophils exhibited very high histamine release values at physiological osmolarity, which increased slightly with osmolarity (340 mOsm). However, further increases in buffer osmolarity to 450 mOsm led to a decrease in histamine release. In the celery-allergic controls, anti-Fc ϵ RI-induced histamine release was very high and did not change when osmolarity increased. In the healthy controls, anti-Fc ϵ RI-induced histamine release remained low in 1 person at all medium osmolarities. In 2 others it was positive, but was not clearly influenced by increasing osmolarity to 340 mOsm. Further increases in medium osmolarity to 450 mOsm resulted in

Table. Spontaneous, Anti-Fc ϵ RI Monoclonal Antibody-Induced and Celery Allergen-Induced Histamine Release From Basophils in Buffers of Increasing Osmolarity

Osmolarity (mOsm)	Spontaneous Histamine Release			Antibody-Induced Histamine Release			Allergen-Induced Histamine Release		
	280	340	450	280	340	450	280	340	450
Patient, %	9.57	15.07	12.16	72.69	84.90	51.32	7.41	16.59	1.46
Mean Healthy controls, %	2.23	3.67	1.22	15.22	15.88	18.56	0.02	0.06	0.7
Mean: Celery-allergic controls, %	2.75	2.7	8.25	87.95	86.55	87.2	16.35	13.25	74.4

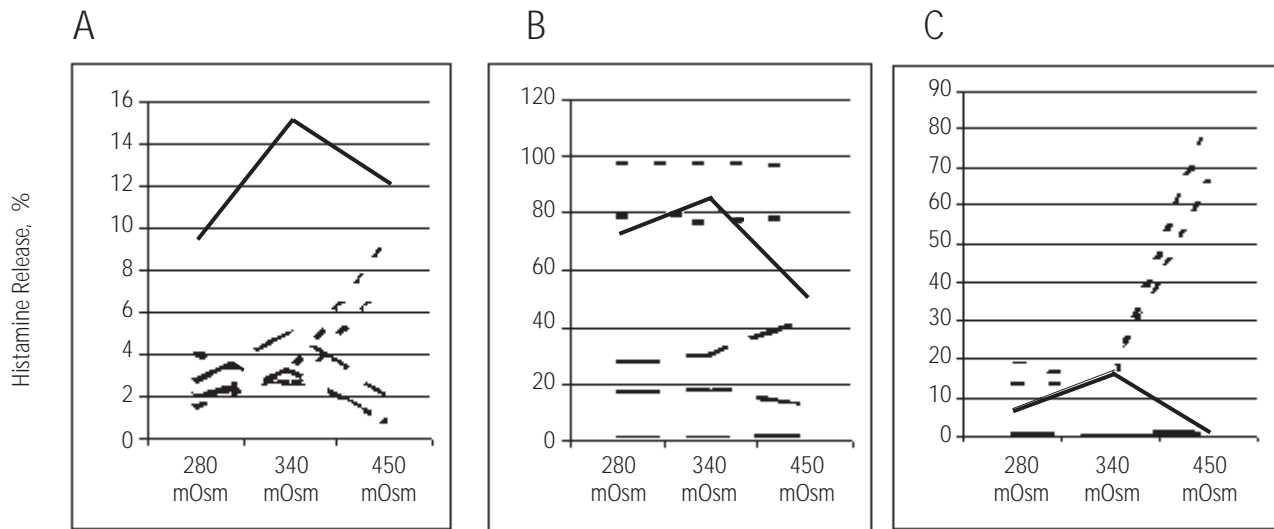


Figure. Spontaneous (A), anti-FcεRI-induced (B) and celery allergen-induced (C) basophil histamine release in the patient (—), celery allergic controls (— —) and healthy controls (— — —) in buffers of increasing osmolarity.

slightly reduced anti-FcεRI-induced histamine release in 1 person and increased anti-FcεRI-induced histamine release in the other. Histamine release upon celery allergen stimulation was positive in the patient and celery-allergic controls. Under physiological conditions, the patient's basophils released 7.4% of histamine. The increase in medium osmolarity up to 340 mOsm resulted in a 2-fold increase in allergen-induced histamine release to 16.6%. A further increase in medium osmolarity to 450 mOsm stopped histamine release. In the celery-allergic controls, increasing medium osmolarity to 340 mOsm resulted in slightly decreased histamine release, but a further increase in medium osmolarity to 450 mOsm produced an extreme increase in HR. In healthy controls, allergen-induced basophil histamine release was always negative under all the experimental conditions. Detailed results are presented in the Table and Figure. In general, only the patient's basophils exhibited an increase in spontaneous, anti-FcεRI-dependent and allergen-dependent histamine release under physiological conditions and a slight increase in medium osmolarity to 340 mOsm.

Discussion

Hyperosmolar activation of basophils has been described elsewhere [3,4,6-8] but its increasing or decreasing effects on the release of histamine may vary according to the cell type tested (mast cell or basophil) and the stimulus used for cell activation. Ours seems to be the first report emphasizing the possible impact of increased histamine releasability on the pathogenic mechanism of FDEIA. Our findings lead us to

hypothesize that this potentially life-threatening anaphylactic reaction might result from increased histamine releasability triggered by physical effort resulting in transient serum hyperosmolarity after exposure to sensitizing food allergen. Since not all food-allergic patients are hypersensitive to exercise, the question remains whether FDEIA serum osmolarity increases during exercise or whether basophils are more sensitive to the effects of hyperosmolarity. The few food-allergic patients not affected by exercise and used as additional controls suggest that the latter is true. If this hypothesis can be proved in further studies, then this *in vitro* method might be helpful in diagnosing FDEIA.

References

1. Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol.* 1979;63:433-4.
2. Aihara Y, Takahashi Y, Kotoyori T, Mitsuda T, Ito R, Aihara M, Ikezawa Z, Yokota S. Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol.* 2001;108:1035-9.
3. Eggleston PA, Kagey-Sobotka A, Schleimer RP, Fink JN. Interaction between hyperosmolar and IgE-mediated histamine release from basophils and mast cells. *Am Rev Respir Dis.* 1984;130:86-91.
4. Nielsen BW, Bjerke T, Damsgaard TM, Herlin T, Thestrup-Pedersen K, Schiøtz PO. Hyperosmolarity selectively enhances IgE-receptor-mediated histamine release from human basophils. *Agents Actions.* 1992;35:170-8.
5. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is ... *J Allergy Clin Immunol.* 2000;106:453-9.

6. Eggleston PA, Kagey-Sobotka A, Proud D, Adkinson NF Jr, Lichtenstein LM. Dissociation of the release of histamine and arachidonic acid metabolism from osmotically activated basophils and human mast lung cells. *Am Rev Respir Dis.* 1990;141:960-4.
7. Stellato C, de Crescenzo G, Patella V, Mastronardi P, Mazzarella B, Marone B. Human basophil/mast cells releasability. XI. Heterogeneity of the effects of contrast media on mediator release. *J Allergy Clin Immunol.* 1996;97:838-50.
8. Tedeschi A, Patella M, Arquati M, Milazzo N, Miadonna A. Ionic regulation of human basophil releasability. III. Effects of Na⁺ and Ca²⁺ on histamine release induced by different stimuli. *Pharmacol Res.* 1994;30:229-41.

■ *Manuscript received December 13, 2007; accepted for publication January 8, 2008.*

■ **Prof. Wojciech Medrala**

Department of Internal Medicine and Allergology
Wroclaw Medical University
Traugutta Str. 57/59
50-417 Wroclaw,
Poland
Fax: +48 71 7332409
E-mail: wojmed@wp.pl