ORIGINAL ARTICLE

Lack of Association Between Aspirin-Triggered 15-Hydroxyeicosatetraenoic Acid Release and Mast Cell/Eosinophil Activation in Nasal Polyps From Aspirin-Sensitive Patients

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Abstract

Background: The mechanism of aspirin sensitivity in patients with asthma and rhinosinusitis has been attributed to arachidonic acid metabolism abnormalities.
Objective: We aimed to test whether aspirin-triggered generation of 15-hydroxyeicosatetraenoic acid (15-HETE) in nasal polyp dispersed cells (NPDCs) from aspirin-sensitive patients is associated with activation of inflammatory cells.
Methods: Polyps were obtained from 11 aspirin-sensitive and 19 aspirin-tolerant patients with chronic rhinosinusitis. NPDCs were stimulated by aspirin or calcium ionophore. Levels of 15-HETE, leukotriene (LT) C_4, eosinophil cationic protein (ECP), and tryptase were measured in NPDC supernatant.
Results: NPDCs from aspirin-sensitive patients contained more eosinophils (14% vs 9%, $P<.05$) and released 2.4-fold more ECP ($P<.01$) at baseline. Stimulation with aspirin (200 μM) resulted in a significant increase in 15-HETE generation only in tissue from aspirin-sensitive patients (mean increase, 82%) but did not induce any increase in the release of LTC_4, ECP, or tryptase. Preincubation with calcium ionophore resulted in significantly enhanced generation of 15-HETE, ECP, tryptase, and LTC_4 in patients from both groups. Incubation of NPDCs with misoprostol inhibited aspirin-induced 15-HETE generation in aspirin-sensitive patients and calcium ionophore–induced 15-HETE, ECP, and tryptase release in both aspirin-sensitive and aspirin-tolerant patients.
Conclusion: Our study demonstrated that aspirin-induced 15-HETE generation in nasal polyps from aspirin-sensitive patients is not associated with activation of mast cells and eosinophils. Misoprostol has a potent inhibitory effect on the activation of cells derived from the site of nasal mucosal inflammation, regardless of sensitivity to aspirin.

Key words: Aspirin sensitivity. Misoprostol. Nasal polyps. 15-HETE

Resumen

Antecedentes: El mecanismo de sensibilidad al ácido acetilsalicílico (AAS) en pacientes con asma y rinosinusitis se ha atribuido a anomalías en el metabolismo del ácido araquidónico.
Objetivo: El objetivo fue estudiar si la producción de ácido 15-hidroxieicosatetraenoico (15 HETE) inducida por AAS en células dispersas de pólipo nasal (NPDC) de pacientes sensibles al AAS está relacionada con la activación de células inflamatorias.
Métodos: Se obtuvieron pólipos de 11 pacientes sensibles al AAS y de 19 pacientes tolerantes al AAS con rinosinusitis crónica. Se estimularon las NPDC mediante AAS o ionóforo de calcio. Se midieron los niveles de 15-HETE, leucotrieno (LT) C4, proteína catiónica del eosinófilo (ECP) y triptasa en el sobrenadante de NPDC.
Resultados: Las NPDC de los pacientes sensibles al AAS contenían más eosinófilos (14% frente al 9%, $p < 0,05$) y liberaron 2,4 veces más ECP ($p < 0,01$) antes de iniciar el estudio. La estimulación con AAS (200 μM) resultó en un aumento significativo de la producción

de 15-HETE únicamente en el tejido de los pacientes sensibles al AAS (aumento medio del 82%), si bien no produjo ningún aumento en la liberación de LTC4, ECP o triptasa. La preincubación con ionóforo de calcio dio lugar a una producción significativamente mayor de 15-HETE, ECP, triptasa y LTC4 en los pacientes de ambos grupos. La incubación de NPDC con misoprostol inhibió la producción de 15-HETE inducida por AAS en los pacientes sensibles al AAS y la liberación de 15-HETE, ECP y triptasa inducida por ionóforo de calcio en los pacientes tanto sensibles como tolerantes al AAS.
Conclusión: En este estudio se demostró que la producción de 15-HETE inducida por AAS en pólipos nasales de pacientes sensibles al AAS no está asociada a la activación de mastocitos y eosinófilos. El misoprostol ejerce un potente efecto inhibitorio sobre la activación de células derivadas del lugar de inflamación de la mucosa nasal, con independencia de la sensibilidad al AAS.

Palabras clave: Sensibilidad al AAS; misoprostol; pólipos nasales; 15-HETE.

Introduction

Aspirin-exacerbated respiratory disease (AERD) is a chronic inflammatory disorder affecting the upper and lower airways. Aspirin-sensitive patients with bronchial asthma usually suffer from chronic rhinosinusitis complicated by nasal polyposis [1]. The mechanism of aspirin sensitivity has been attributed to abnormalities of arachidonic acid metabolism. According to the cyclooxygenase (COX) theory of aspirin intolerance, inhibition of COX-1 by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) followed by suppression of prostaglandin (PG) E_2 synthesis triggers the activation of inflammatory cells, subsequent release of inflammatory mediators (histamine, PGD_2, tryptase, eosinophil cationic protein [ECP]), and increased generation of cysteinyl leukotrienes (CysLT) [2,3]. Patients with AERD have higher exhaled air CysLT levels and higher baseline levels of CysLT in saliva, sputum, blood (ex vivo), and urine than aspirin-tolerant individuals [4]. CysLT levels and relevant enzyme expression (5-lipoxygenase [LO], LTC_4 synthase) are increased in the nasal polyps of aspirin-sensitive patients [5], and CysLT1 receptor is overexpressed in aspirin-sensitive individuals [6].

Nasal polyp cells from aspirin-sensitive patients generated significantly less PGE_2 and showed lower expression of COX-2 mRNA and PGE_2 receptor mRNA than aspirin-tolerant patients, suggesting a deficient regulatory role of PGE_2 in this group [5,7-9]. In a previous study, we demonstrated that incubation of nasal epithelial cells and peripheral blood leukocytes with aspirin resulted in significantly increased hydroxyeicosatetraenoic acid (15-HETE) generation in aspirin-sensitive patients, but had no effect on 15-HETE generation in aspirin-tolerant patients [10,11].

We tested whether aspirin triggered 15-HETE generation in nasal polyp dispersed cells (NPDC) from aspirin-sensitive patients and whether this release was associated with activation of inflammatory cells (mast cells and eosinophils). We also assessed modulation of specific (aspirin-triggered) release and nonspecific (calcium ionophore–induced) release of mediators from NPDCs by a synthetic PGE_1 analog.

Material and Methods

Patients

Nasal polyps were obtained from 11 aspirin-sensitive and 19 aspirin-tolerant patients with chronic rhinosinusitis undergoing elective nasal surgery for reasons unrelated to the goals of this study. Rhinosinusitis was diagnosed based on a clinical history of recurrent symptoms, and presence of nasal polyps was confirmed by rhinoscopy, computed tomography, or both. Bronchial asthma was diagnosed based on the Global Initiative for Asthma guidelines in 13 patients (11 of whom were sensitive to aspirin) [12]. A positive history of bronchial and/or nasal reaction to aspirin or other NSAIDs was confirmed by positive nasal or inhalation challenge with lysine aspirin. Atopy was defined based on a positive personal history of allergic respiratory symptoms and positive skin prick test results (wheal >3 mm) with a panel of inhalant allergens. The clinical characteristics of both groups are summarized in Table 1.

Table 1. Characteristics of Aspirin-Sensitive and Aspirin-Tolerant Patients

	Aspirin-Sensitive	Aspirin-Tolerant
n	11	19
Men/Women	8/3	13/6
Age, y		
Mean	50	58
Min-Max	36-78	36-82
Patients with bronchial asthma	11	2
Patients with atopy	11	1
Number of polypectomies		
Median	4	1
Min-Max	1-6	1-11

None of the patients had received oral or intranasal corticosteroids for at least 4 weeks before surgery. The local medical ethics committee approved the study, and all patients gave their informed consent to participate.

Tissue Handling and NPDC Preparation

After surgery, nasal polyps were placed in Medium 199 at 0°C (Sigma, St. Louis, Missouri, USA) and immediately transported to the laboratory in a thermal insulation container (temperature, 4-6°C). Polyps were dissected with scissors into pieces of approximately 2 mm^3. Dissected polyp tissue was placed in RPMI 1640 culture medium (Sigma) containing 0.75 mg/mL of hyaluronidase (Sigma), 1.5 mg/mL collagenase (Sigma), and 2 mg/mL protease type XIV (Sigma) for 120

minutes, as described elsewhere [13]. After dispersion, cells were filtered and resuspended in 15 mL of Medium 199 (Sigma), washed 3 times to remove the enzymes, and finally cultured at a concentration of 1×10^6 cells/mL in Medium 199. The differential count was performed in a Shandon Cytospin device (Shandon Scientific Ltd, Runcorn, UK) with preparations stained using the May-Grünwald-Giemsa technique and chromotrope 2R to detect eosinophils. During experiments, cells were preincubated with medium or misoprostol (100 nM, 10 nM, 1 nM) (Cayman Chemical, Ann Arbor, Michigan, USA) for 60 minutes and then stimulated with lysine aspirin (2 μM, 20 μM, 200 μM) or calcium ionophore (10^{-5}M) for 60 minutes at 37°C. Mediators were measured in supernatants collected after 60 minutes' incubation with medium or respective stimuli and stored at –70ºC.

Measurement of Mediators

The 15-HETE concentration in cell supernatants was measured using specific enzyme-linked immunosorbent assays (ELISA) (Assay Designs Inc, Ann Arbor, Michigan, USA). ECP and tryptase release was assayed using the Pharmacia UniCap system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden), and LTC_4 generation was measured using specific ELISA (Cayman Chemical).

Statistical Analysis

Mediator stimulation and inhibition data were analyzed using the Wilcoxon signed rank test. Mediator release between aspirin-sensitive and aspirin-tolerant patients was compared using the nonparametric Mann-Whitney test preceded by an evaluation of normality. Correlation coefficients were calculated using the Spearman rank correlation coefficient method. A P value <.05 was considered statistically significant.

Results

Baseline Mediator Release From NPDCs

NPDCs from aspirin-sensitive patients contained more eosinophils (14% vs 9% of cells, P<.05) and released 2.4-fold more ECP at baseline (P<.01) than tissue from aspirin-tolerant patients. Baseline levels of 15-HETE, tryptase, and LTC_4 were similar in both groups.

Effects of Aspirin on Mediator Release From NPDCs

Stimulation with aspirin 200 μM (but not 2 μM or 20 μM) resulted in a significant increase in 15-HETE generation only in tissue from aspirin-sensitive patients (mean increase, 127%; P<.05) (Table 2, Figure 1). Analysis of individual data demonstrated a ≥50% increase in 15-HETE generation after 200 μM in 6 of 8 aspirin-sensitive patients and after 20 μM in 3 of 8 aspirin-sensitive patients. Aspirin caused a ≥50% increase in 15-HETE generation in only 2 of 12 aspirin-tolerant patients (The highest increase was 70% in 1 patient.) Incubation of NPDCs with aspirin for 60 minutes did not induce any increase in the release of LTC_4, ECP, or tryptase in either group (Table 2).

Although misoprostol did not affect baseline release of 15-HETE, it significantly inhibited aspirin-induced 15-HETE generation in NPDCs from aspirin-sensitive patients, with maximum inhibition observed for the lowest 2 concentrations (mean inhibition was 100%, 100%, and 45% for 1 nM, 10 nM, and 100 nM of misoprostol, respectively; P<.05) (Figure 2).

Table 2. Effect of Increasing Concentrations of Aspirin on Release of Mediators From Nasal Polyp Dispersed Cells[a]

	Medium	Lysine aspirin, μM		
		2	20	200
Aspirin-sensitive (n=8-11)				
15-HETE, pg/mL	10 984 (1717)	8420 (1440)	11 558 (1826)	19 292 (1787)[b]
LTC_4, pg/mL	75.3 (34)	89.5 (32)	75.3 (20)	89.28 (34)
Tryptase, μg/L	8.6 (2)	ND	ND	7.2 (1)
ECP, μg/L	151.0 (33)	ND	ND	164.3 (41)
Aspirin-tolerant (n=12-19)				
15-HETE, pg/mL	11 636 (1167)	9786 (1192)	10 267 (1138)	12 341 (1354)
LTC_4, pg/mL	65.2 (27)	66.1 (23)	62.7 (24)	54.9 (17.8)
Tryptase, μg/L	7.2 (1)	ND	ND	7.1 (2)
ECP, μg/L	76.1 (24)	ND	NDF	81.3 (30)

Abbreviation: ECP, eosinophil cationic protein; HETE, hydroxyeicosatetraenoic acid; LT, leukotriene; ND, not determined.
[a]Values expressed as mean (SEM)
[b]P<.05, as compared to medium.

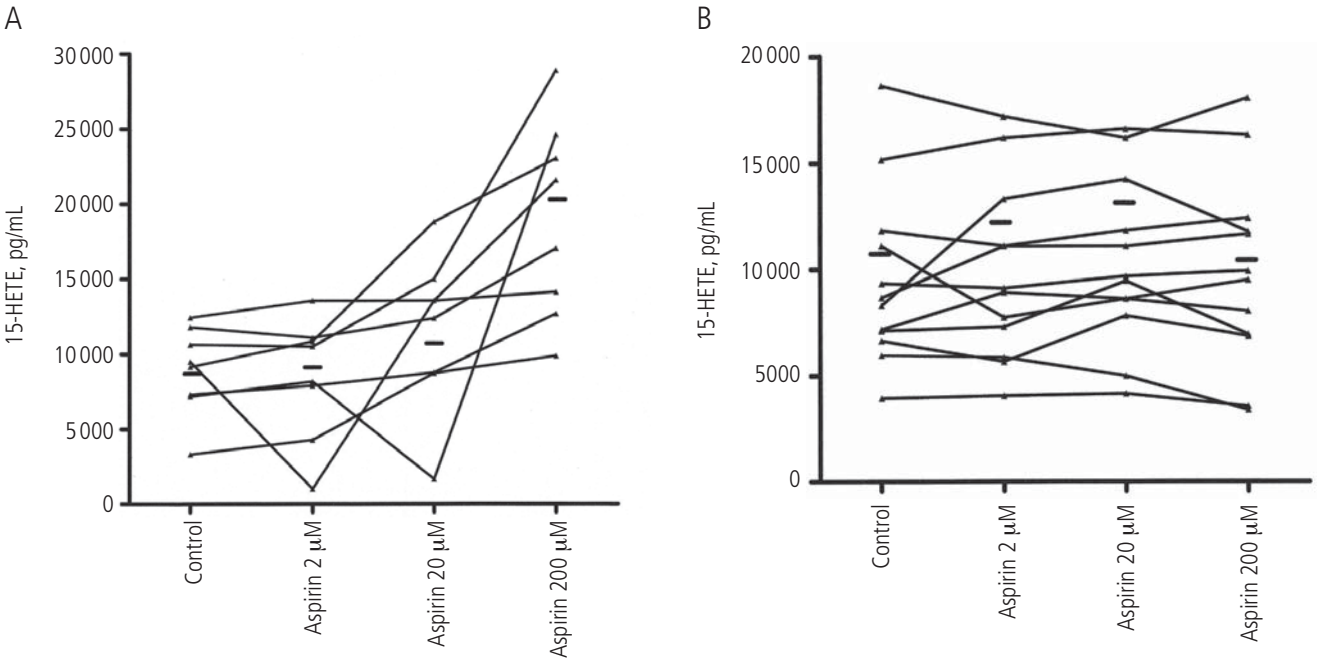

Figure 1. A, Effect of lysine aspirin on 15-HETE generation in nasal polyp dispersed cells in aspirin-sensitive (n=8) patients. B, Effect of lysine aspirin on 15-HETE generation in nasal polyp dispersed cells in aspirin-tolerant patients (n=12). HETE indicates hydroxyeicosatetraenoic acid.

Calcium Ionophore–Induced Mediator Release and Modulation by Misoprostol

Stimulation of NPDCs with 10^{-5}M calcium ionophore resulted in a significant enhancement of 15-HETE, LTC_4, ECP, and tryptase release in both groups (Table 3).

Although the relative increases in mediator concentration tended to be higher in samples from aspirin-sensitive patients than aspirin-tolerant patients for 15-HETE (178% vs 113%) and LTC_4 (1589% vs 775%) and lower for ECP (83% vs 205%) and tryptase (225% vs 298%), the differences were not statistically significant, and the mean concentrations of calcium ionophore–induced mediators were similar in both groups. Misoprostol at a concentration of 1 nM (but not 10 nM or 100 nM) significantly decreased calcium ionophore–induced

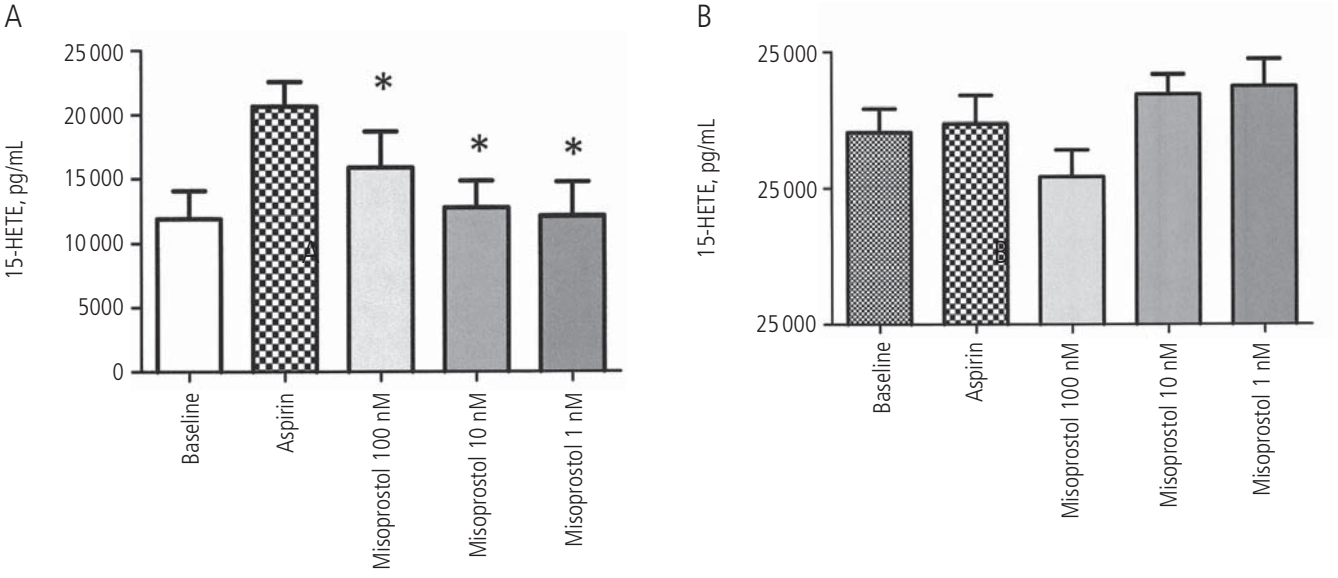

Figure 2. A, Effect of misoprostol on aspirin induced 15-HETE generation in nasal polyp dispersed cells from aspirin-sensitive patients (n=8). B, Effect of misoprostol on aspirin induced 15-HETE generation in nasal polyp dispersed cells from aspirin-tolerant patients (n=11). HETE indicates hydroxyeicosatetraenoic acid.

Table 3. Inhibitory Effect of Misoprostol on Calcium Ionophore–Induced Release of Mediators From Nasal Polyp Dispersed Cells in Aspirin-Sensitive and Aspirin-Tolerant Patients[a]

Mediator	Aspirin-Sensitive	Aspirin-Tolerant	*P*[b]
15-HETE, ng/mL	n=8	n=10	
Basal	10.4 (7.1-25.9)	13.7 (3.9-21.7)	.23
Calcium ionophore	30.7 (10.8-46.5)	25.1 (1.4-40.9)	.5
Calcium ionophore + misoprostol	19.0 (11.5-44.0)[c]	20.1 (11.4-40.1)[c]	1.0
% inhibition	93	30	
ECP, µg/L n=6	n=7		
Basal	139.5 (49.0-278.0)	56.8 (12.4-162.4)	.01
Calcium ionophore	204.0 (176.0-298.0)	194.6 (28.4-324.0)	.53
Calcium ionophore + misoprostol	195.0 (80.0-326.0)[c]	134.0 (24.5-258.0)[c]	.53
% inhibition	39	26	
Tryptase, µg/Ln=6	n=7		
Basal	7.8 (1.3-18.3)	6.1 (3.3-14.8)	.73
Calcium ionophore	22.8 (5.4-67.5)	13.1 (5.3-81.8)	1.0
Calcium ionophore + misoprostol	12.5 (2.1-55.2)[c]	13.5 (5.5-60.2)[c]	.73
% inhibition	64	42	

Abbreviations: ECP, eosinophil cationic protein; HETE, hydroxyeicosatetraenoic acid.
[a]Data are expressed as median (range).
[b]Difference between groups.
[c]Significantly inhibited as compared to calcium ionophore alone ($P<.05$).

15-HETE generation (mean inhibition was 93% and 30% in NPDCs from aspirin-sensitive and aspirin-tolerant patients, respectively). Misoprostol at 1 nM significantly inhibited calcium ionophore–induced ECP release (39% vs 26%) and tryptase release (64% vs 42%) in aspirin-sensitive and aspirin-tolerant tissue, respectively.

The effect of misoprostol on LTC_4 release was not studied. No association was established between the magnitude of calcium ionophore–stimulated release and the inhibitory effect of misoprostol on the respective mediators.

Discussion

This study demonstrated that aspirin-induced 15-HETE generation induced specifically by aspirin in cells from aspirin-sensitive—but not aspirin-tolerant—patients is not accompanied by release of other inflammatory mediators (tryptase, ECP, LTC_4) typically associated with aspirin-induced respiratory reaction in the nose [14-18]. These observations were possible thanks to the experimental model used (ie, NPDC), which, as opposed to models previously used by our group (isolated nasal polyp epithelial cells [7] and leukocytes [10,19]), enabled us to study the effect of aspirin stimulation in tissue containing several types of inflammatory cells potentially involved in aspirin-induced reactions. We showed that aspirin-triggered in vitro generation of 15-HETE from isolated nasal polyp epithelial cells and peripheral blood leukocytes and was quite specific for patients with a history of aspirin-induced asthma/rhinosinusitis.

The present study confirms the specificity of aspirin-triggered 15-HETE release; however, it casts some doubt on the relevance of 15-HETE release for the pathogenic mechanism of aspirin-induced nasal reaction in sensitive patients. Although cells triggered by aspirin in vivo that are responsible for the development of symptoms have not been identified, nasal reaction induced by aspirin in the sensitive patient is accompanied by release of tryptase, LTC_4, and ECP, strongly suggesting activation of mast cells and eosinophils and implicating these cells in the pathophysiology of reaction. Failure to detect mast cells and eosinophil activation after aspirin challenge in an NPDC-based model could result from a technical error. However, tryptase, LTC_4, and ECP were detected in baseline samples (cells incubated with medium), and the release of mediators could be further increased by a nonspecific trigger (calcium ionophore), indicating that our experimental model could reliably detect activation of mast cells and eosinophils.

The cellular source of aspirin-triggered 15-HETE in NPDCs has not been identified; however, several of the cells present in our tissue preparation are capable of generating this mediator. We might assume that 15-HETE was released from epithelial cells, which are the major source of this mediator and were previously demonstrated to generate 15-HETE after challenge with aspirin [7]. Selective activation of epithelial cells by aspirin in this model would explain the lack of release of other mediators upon challenge with aspirin. However, it is difficult to compare this observation with our previous observation of 15-HETE triggering by aspirin in peripheral blood leukocytes of aspirin-sensitive patients with asthma.

Our previous study demonstrated that aspirin-triggered 15-HETE generation in aspirin-sensitive patients can be inhibited by the synthetic PGE analogs misoprostol and sulproston and, more specifically, by specific PGE_{1-3} receptor agonists, suggesting a critical role of PGE in the modulation of 15-HETE release [11]. These observations are consistent with the PG/COX pathway hypothesis and clinical studies showing that inhaled PGE_2 and PG analogs protected against aspirin-induced asthma attacks in aspirin-sensitive patients [1,20,21]. In the present study, we confirmed that misoprostol significantly inhibited aspirin-triggered 15-HETE release. However, in the same model, misoprostol significantly inhibited release of 15-HETE, ECP, and tryptase triggered by a nonspecific stimulus (calcium ionophore), indicating significant inhibition of eosinophil and mast cell activation in both aspirin-sensitive and aspirin-tolerant patients. Therefore, the inhibitory effect of misoprostol on aspirin-triggered 15-HETE generation may reflect the cell-stabilizing activity of PGE acting via PGE receptors, rather than specific modulation of arachidonic acid metabolism in aspirin-sensitive patients. The inhibitory effect of misoprostol on calcium ionophore–induced 15-HETE, ECP, and tryptase release was observed in both aspirin-sensitive and aspirin-tolerant patients, and, although the degree of inhibition tended to be more pronounced in cells from aspirin-sensitive patients than aspirin-tolerant patients, the differences were not significant. Interestingly, using isolated bone marrow mast cells, Wang et al [22] demonstrated that PGE_2 suppressed LTC_4 release only in cells isolated from aspirin-sensitive patients but not in aspirin-tolerant patients. These observations could argue for a more important regulatory role of PGE and its receptors in the pathophysiology of chronic inflammation in aspirin-sensitive patients than in aspirin-tolerant patients.

As our study compared baseline and calcium ionophore–triggered mast cell (tryptase) and eosinophil (ECP) mediators released in nasal polyp tissue from clearly defined aspirin-sensitive and aspirin-tolerant patients, it also gives some insight into the pathophysiology of chronic upper airway inflammation. A higher percentage of eosinophils and a 2.4-fold higher concentration of ECP in cell supernatants clearly confirm the more eosinophilic character of nasal polyps in aspirin-sensitive patients [5,23,24]. The higher eosinophilic infiltration of nasal polyps in aspirin-sensitive patients has been documented in several studies, although the exact mechanism is not understood. In addition to the putative role of interleukin 5 and chemokines [24,25], a novel mechanism of eosinophil recruitment and activation involving eoxins derived from the 15-lipoxygenase (LOX) pathway has been described [26]. Eoxins may be a cause of eosinophil activation in AERD patients, since severe asthma and aspirin-intolerant asthma markedly enhanced the 15-LOX pathway [27]. Overexpression of 15-LOX1 in bronchial epithelium accompanied by increased 15(S)-HETE expression was observed in bronchoalveolar lavage fluid after allergen challenge in asthmatics [28]. Moreover, elevated expression of 15-LOX1 in human bronchial epithelial cells leading to increased release of chemokines suggests that increased expression and activity of 15-LOX1 in lung epithelial cells plays an important role in the pathogenesis of asthma [29]. Eoxins are released in the nasal polyps of allergic individuals [26] and warrant further testing after aspirin challenge.

Baseline and stimulated release of LTC_4 were similar in nasal polyp cells from both subpopulations of patients, arguing against the hypothesis that mucosal inflammation in aspirin-sensitive patients is CysLT-driven [4]. These findings suggest that the overproduction of CysLT detected in the urine of aspirin-sensitive patients may reflect an increase in the total number of CysLT-producing cells such as eosinophils and mast cells rather than CysLT overproduction at the cellular level.

In summary, this study demonstrated that specific triggering of 15-HETE generation by aspirin in the nasal polyp tissue of patients with AERD is not accompanied by activation of mast cells and eosinophils. Activation of PGE receptors has a potent inhibitory effect on activation of cells derived from the site of nasal mucosal inflammation, regardless of the presence of sensitivity to aspirin.

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References

1. Szczeklik A, Sanak M. The broken balance in aspirin hypersensitivity. Eur J Pharmacol. 2006;533:145-55.
2. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. J Allergy Clin Immunol. 2006;118:773-86; quiz 787-8.
3. Picado C. Mechanisms of aspirin sensitivity. Curr Allergy Asthma Rep. 2006;6:198-202.
4. Gaber F, Daham K, Higashi A, Higashi N, Gulich A, Delin I, James A, Skedinger M, Gyllfors P, Nord M, Dahlen SE, Kumlin M, Dahlen B. Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and blood from patients with aspirin-intolerant asthma. Thorax. 2008;63:1076-82.
5. Pérez-Novo CA, Watelet JB, Claeys C, Van Cauwenberge P, Bachert C. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. J Allergy Clin Immunol. 2005;115:1189-96.
6. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med. 2002;347:1493-9.
7. Kowalski ML, Pawliczak R, Wozniak J, Siuda K, Poniatowska M, Iwaszkiewicz J, Kornatowski T, Kaliner MA. Differential metabolism of arachidonic acid in nasal polyp epithelial cells cultured from aspirin-sensitive and aspirin-tolerant patients. Am J Respir Crit Care Med. 2000;161:391-8.
8. Pujols L, Mullol J, Alobid I, Roca-Ferrer J, Xaubet A, Picado C. Dynamics of COX-2 in nasal mucosa and nasal polyps from aspirin-tolerant and aspirin-intolerant patients with asthma. J Allergy Clin Immunol. 2004;114:814-9.
9. Ying S, Meng Q, Scadding G, Parikh A, Corrigan CJ, Lee TH. Aspirin-sensitive rhinosinusitis is associated with reduced E-prostanoid 2 receptor expression on nasal mucosal inflammatory cells. J Allergy Clin Immunol. 2006;117:312-8.
10. Kowalski ML, Ptasinska A, Bienkiewicz B, Pawliczak R,

DuBuske L. Differential effects of aspirin and misoprostol on 15-hydroxyeicosatetraenoic acid generation by leukocytes from aspirin-sensitive asthmatic patients. J Allergy Clin Immunol. 2003;112:505-12.
11. Jedrzejczak-Czechowicz M, Lewandowska-Polak A, Bienkiewicz B, Kowalski ML. Involvement of 15-lipoxygenase and prostaglandin EP receptors in aspirin-triggered 15-hydroxyeicosatetraenoic acid generation in aspirin-sensitive asthmatics. Clin Exp Allergy. 2008;38:1108-16.
12. GINA Global Strategy for Asthma Management and Prevention, 2006 NHI Publications No 02-3659. GINA update 2008. http://www.ginasthma.org.
13. Lebel B, Crampette L, Vergnes C, Campbell AM, Bousquet J. Inhibition of mediator release from dispersed nasal polyp cells by cyclosporin A. Int Arch Allergy Immunol. 1998;116:284-7.
14. Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Rubin P, Cohn J, White MV, Igarashi Y, Kaliner MA, Drazen JM, Israel E. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. J Allergy Clin Immunol. 1994;94:1046-56.
15. Kowalski ML, Sliwinska-Kowalska M, Igarashi Y, White MV, Wojciechowska B, Brayton P, Kaulbach H, Rozniecki J, Kaliner MA. Nasal secretions in response to acetylsalicylic acid. J Allergy Clin Immunol. 1993;91:580-98.
16. Kowalski ML, Grzegorczyk J, Wojciechowska B, Poniatowska M. Intranasal challenge with aspirin induces cell influx and activation of eosinophils and mast cells in nasal secretions of ASA-sensitive patients. Clin Exp Allergy. 1996;26:807-14.
17. Mita H, Endoh S, Kudoh M, Kawagishi Y, Kobayashi M, Taniguchi M, Akiyama K. Possible involvement of mast-cell activation in aspirin provocation of aspirin-induced asthma. Allergy. 2001;56:1061-7.
18. Kupczyk M, Antczak A, Kuprys-Lipinska I, Kuna P. Lipoxin A4 generation is decreased in aspirin-sensitive patients in lysine-aspirin nasal challenge in vivo model. Allergy. 2009;64:1746-52.
19. Kowalski ML, Ptasinska A, Jedrzejczak M, Bienkiewicz B, Cieslak M, Grzegorczyk J, Pawliczak R, DuBuske L. Aspirin-triggered 15-HETE generation in peripheral blood leukocytes is a specific and sensitive Aspirin-Sensitive Patients Identification Test (ASPITest). Allergy. 2005;60:1139-45.
20. Szczeklik A, Mastalerz L, Nizankowska E, Cmiel A. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. Am J Respir Crit Care Med. 1996;153:567-71.
21. Szmidt M, Wasiak W. The influence of misoprostol (synthetic analogue of prostaglandin E1) on aspirin-induced bronchoconstriction in aspirin-sensitive asthma. J Investig Allergol Clin Immunol. 1996;6:121-5.
22. Wang XS, Wu AY, Leung PS, Lau HY. PGE suppresses excessive anti-IgE induced cysteinyl leucotrienes production in mast cells of patients with aspirin exacerbated respiratory disease. Allergy. 2007;62:620-7.
23. Kowalski ML, Lewandowska A, Wozniak J, Makowska J, Jankowski A, DuBuske L. Inhibition of nasal polyp mast cell and eosinophil activation by desloratadine. Allergy. 2005;60:80-5.
24. Perez-Novo CA, Kowalski ML, Kuna P, Ptasinska A, Holtappels G, van Cauwenberge P, Gevaert P, Johannson S, Bachert C. Aspirin sensitivity and IgE antibodies to Staphylococcus aureus enterotoxins in nasal polyposis: studies on the relationship. Int Arch Allergy Immunol. 2004;133:255-60.
25. Park HS, Jung KS, Shute J, Roberts K, Holgate ST, Djukanovic R. Allergen-induced release of GM-CSF and IL-8 in vitro by nasal polyp tissue from atopic subjects prolongs eosinophil survival. Eur Respir J. 1997;10:1476-82.
26. Feltenmark S, Gautam N, Brunnstrom A, Griffiths W, Backman L, Edenius C, Lindbom L, Bjorkholm M, Claesson HE. Eoxins are proinflammatory arachidonic acid metabolites produced via the 15-lipoxygenase-1 pathway in human eosinophils and mast cells. Proc Natl Acad Sci U S A. 2008;105:680-5.
27. Zhao J, Maskrey B, Balzar S, Chibana K, Mustovich A, Hu H, Trudeau JB, O'Donnell V, Wenzel SE. Interleukin-13-induced MUC5AC is regulated by 15-lipoxygenase 1 pathway in human bronchial epithelial cells. Am J Respir Crit Care Med. 2009;179:782-90.
28. Chu HW, Balzar S, Westcott JY, Trudeau JB, Sun Y, Conrad DJ, Wenzel SE. Expression and activation of 15-lipoxygenase pathway in severe asthma: relationship to eosinophilic phenotype and collagen deposition. Clin Exp Allergy. 2002;32:1558-65.
29. Liu C, Xu D, Liu L, Schain F, Brunnstrom A, Bjorkholm M, Claesson HE, Sjoberg J. 15-Lipoxygenase-1 induces expression and release of chemokines in cultured human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2009;297:L196-203.

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