Eur Respir J, 1993, 6, 1468–1473
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

Airway responsiveness to leukotriene C_4 (LTC_4), leukotriene E_4 (LTE_4) and histamine in aspirin-sensitive asthmatic subjects

P.E. Christie*, M. Schmitz-Schumann**, B.W. Spur+, T.H. Lee+

Airway responsiveness to leukotriene C_4 (LTC_4), leukotriene E_4 (LTE_4) and histamine in aspirin-sensitive asthmatic subjects. P.E. Christie, M. Schmitz-Schumann, B.W. Spur, T.H. Lee. ©ERS Journals Ltd 1993.

ABSTRACT: We wanted to determine whether the airway response to inhaled leukotriene C_4 (LTC_4) is similar to inhaled leukotriene E_4 (LTE_4) in aspirin-sensitive asthma and, therefore, determined airway responsiveness to histamine, LTC_4 and LTE_4 in seven aspirin-sensitive subjects and 13 control asthmatic subjects, who were tolerant of aspirin.

The concentration of inhaled lysine-aspirin which produced a 15% fall in forced expiratory volume in one second (FEV_1) (PC_{15}) was determined in aspirin-sensitive asthmatic subjects. The dose of histamine, LTC_4 and LTE_4 which produced a 35% fall in specific airways conductance (PD_{35}sGaw) was determined by linear interpolation from the log dose response curve.

There was no correlation between the PC_{15} for lysine-aspirin and the airway reactivity to inhaled LTC_4 or LTE_4. There was no difference in airway response to histamine and LTC_4 between any of the groups of asthmatic subjects. There was a rank order of potency LTC_4>LTE_4>histamine in both groups, with LTC_4 approximately 1,000 fold more potent than histamine in both groups. Aspirin-sensitive asthmatic subjects were significantly more responsive to LTE_4 ($p=0.02$) than aspirin-tolerant asthmatic subjects. The relative responsiveness of LTE_4 to histamine (PD_{35} histamine/PD_{35} LTE_4) was significantly greater in aspirin-sensitive asthmatic subjects compared to aspirin-tolerant asthmatic subjects ($p=0.05$). There was no difference in relative responsiveness of LTC_4 to histamine between aspirin-sensitive or aspirin-tolerant asthmatic subjects.

We conclude that the airways of aspirin-sensitive asthmatic subjects demonstrate a selective hyperresponsiveness to LTE_4, which is not observed for LTC_4.

Eur Respir J., 1993, 6, 1468–1473.

*Swiss Institute for Allergy and Asthma Research, Davos, Switzerland. **Hochgebirgsklinik, Wolfgang-Davos, Switzerland. +Dept of Allergy and Allied Respiratory Disorders, UMDS, Guy's Hospital, London, UK.

Correspondence: T.H. Lee
Dept of Allergy and Allied Respiratory Disorders
4th Floor, Hunt's House
Guy's Hospital
London SE1 9RT
UK

Keywords: Airways
aspirin
asthma
leukotriene
receptor

Received: January 15 1993
Accepted after revision June 2 1993

Arachidonic acid, released from cell membrane phospholipids by the action of phospholipase A_2, may be metabolized by the cyclo-oxygenase pathway to generate prostaglandins and thromboxane A_2, or by the 5-lipoxygenase pathway to generate the leukotrienes (LT), LTB_4, LTC_4, LTD_4 and LTE_4 [1, 2]. The sulphidopeptide leukotrienes LTC_4, LTD_4 and LTE_4 comprise the activity previously recognized as slow-reacting substance of anaphylaxis (SRS-A)[3, 4]. *In vitro* these compounds are potent contractile agonists for nonvascular smooth muscle, and in humans are potent bronchoconstrictor agonists when inhaled [5].

A proportion of asthmatic subjects develop bronchospasm following ingestion of aspirin, which may be accompanied by naso-ocular symptoms, and they are termed aspirin-sensitive. Sulphidopeptide leukotrienes may play a role in aspirin-sensitive asthma. The airways of aspirin-sensitive asthmatic subjects demonstrate increased airway response to inhaled LTE_4, compared to asthmatic subjects who are aspirin-tolerant [6]. Following desensitization with aspirin, the airway response to inhaled LTE_4 is reduced, whilst the airway response to histamine remains unchanged [6]. Baseline urinary LTE_4 concentrations are elevated in aspirin-sensitive asthmatic subjects compared to aspirin-tolerant subjects, and there is further release of LTE_4 following oral aspirin challenge in aspirin-sensitive asthmatic subjects [7, 8]. Prior inhalation of the leukotriene receptor antagonist SK&F 104353 attenuates aspirin-induced bronchoconstriction in aspirin-sensitive subjects [9].

It is unknown whether the airway response to inhaled LTC_4 is similar to inhaled LTE_4 in aspirin-sensitive asthma. This study compares the airway responses to inhaled LTC_4, LTE_4 and histamine, between aspirin-sensitive and aspirin-tolerant asthmatic subjects.

Subjects

Seven aspirin-sensitive subjects (4 male, 3 female, aged 23–55 yrs), and 13 non-aspirin-sensitive asthmatic subjects (7 males, 6 female, aged 23–52 yrs), of whom seven were non-atopic and six were atopic, were studied (table 1). Asthma was defined by a history of episodic wheezing and a greater than 20% reversibility of resting forced expiratory volume in one second (FEV_1) following 400 μg

Table 1. – Patient characteristics and treatment

Subject No.	Age yrs	Sex	Atopy	FEV_1 % pred	Treatment	lys-asp mg·ml^{-1}
Aspirin-sensitive asthmatic subjects						
1	42	M	-	85	AB	2.5
2	23	F	+	92	AB	2.5
3	34	M	+	82	ABC	1.25
4	23	F	+	97	ABC	2.5
5	55	F	-	95	AB	5.0
6	51	M	+	81	AB	2.5
7	46	M	-	78	ABD	1.25
Mean	39			87		2.5
SEM	4.8			2.8		0.4
Aspirin-tolerant asthmatic subjects						
1	45	M	-	129	AB	
2	18	M	-	97	AB	
3	22	F	-	82	A	
4	41	F	-	107	AB	
5	24	F	-	99	A	
6	52	M	-	105	A	
7	45	M	-	88	A	
8	48	F	+	92	AB	
9	48	M	+	112	A	
10	20	F	+	89	AB	
11	43	M	+	86	AB	
12	40	F	+	107	AB	
13	28	M	+	100	AB	
Mean	36			99		
SEM	3.3			3.5		

A: inhaled albuterol, 200 μg *t.d.s., prn*; B: inhaled corticosteroid, 200 μg *b.d.*; C: theophylline, 500 mg *b.d.*; D: prednisolone, 8 mg orally *q.d.*; FEV_1: forced expiratory volume in one second; lys-asp: lysine-aspirin (inhalation challenge).

inhaled salbutamol. The % predicted baseline FEV_1 was 87±2.8% (mean±SEM) and 99±3.5% in the aspirin-sensitive asthmatic and control (aspirin-tolerant) asthmatic subjects, respectively. Aspirin-sensitive asthma was confirmed by the presence of a positive lysine-aspirin inhalation challenge. Atopy was defined by positive skin prick tests to at least two common aeroallergens: grass pollen, tree pollen, cat dander, dog hair, *Dermatophagoides pteronyssinus* and *D. farinae* and total serum immunoglobulin E (IgE) level >160 kU·ml^{-1}. Subjects had not taken antihistamines or cromolyn in the month prior to the study, and no subject had experienced an upper respiratory tract infection in the preceding month or during the study. Permitted medication, which remained unchanged during the study, included inhaled β-agonist and inhaled corticosteroid. Aspirin-sensitive asthmatic subjects Nos. 3 and 4 were receiving theophylline, 500 mg twice daily, and subject No. 7 was receiving oral prednisolone, 8 mg daily. Medication was withheld 8 h prior to provocation prior to each study day. Each subject underwent inhalation challenge with lysine-aspirin to exclude the presence of aspirin sensitivity.

The study protocol was approved by the Hochgebirgsklinik, Davos-Wolfgang Ethics Committee and each subject gave informed consent.

Study design

Subjects were recruited into the study following clinical assessment, skin prick tests blood sampling and lysine-aspirin inhalation challenge. Subjects attended the laboratory on three separate occasions, separated by at least a one week interval, when inhalation challenges with histamine, LTC_4 or LTE_4 were performed in a randomized fashion. Histamine challenge was performed single-blind, whereas LTC_4 and LTE_4 were performed double-blind.

Methods

Measurements of airway calibre

Measurements of specific airways conductance (sGaw) were made in a total body plethysmograph linked to a digital computer (Bodytest, Jaeger Ltd). Provided baseline sGaw was >0.7 s^{-1}·kPa^{-1}, inhalation challenge with agonist proceeded. There was no significant difference in baseline sGaw values in individual subjects on separate study days.

Inhalation challenge

Inhalation challenges were performed using the Asthma Provocation System (APS) Jaeger dosimeter which delivers compressed air at a pressure of 1.6 bar (22.8 psi) for a duration of 0.6 s from the start of each breath. Under these conditions, the nebulizer delivers droplets with a mass median aerodynamic diameter of 1.9 μm and the output of the nebulizer is 5.8 μl·breath^{-1}. Following baseline measurements of sGaw, subjects inhaled control solution (10 breaths of phosphate buffered saline (PBS) for leukotriene challenges, and 5 breaths of normal saline for histamine challenge). Each inhalation started at functional residual capacity and terminated at approximately 70% baseline vital capacity; a 5 s breathhold was maintained at the end of each inhalation. If the decrease in sGaw was <10% from baseline value, subjects underwent inhalation challenge with histamine, LTC_4 or LTE_4.

Histamine challenge

Serial twofold increasing concentrations of histamine chloride (Fluela apotheke, Davos, Switzerland) were inhaled from a concentration of 0.03 mg·ml^{-1} (0.16 mM). Specific airways conductance was measured 2 min after each inhalation, and doubling concentrations were administered until the sGaw had fallen by more than 35%.

Inhalation challenge with LTC_4 and LTE_4

LTC_4 and LTE_4 were prepared by total chemical synthesis, as described previously, and frozen under argon at

-70°C [3]. Each leukotriene was analysed before inhalation challenge by reverse phase high performance liquid chromatography (RP-HPLC), on a 10 μm C_{18} ultrasil-ODS column (4.6×250 mm; Beckman Instruments Inc., Berkley, CA, USA), at a flow rate of 1 ml·min^{-1} with 65% methanol (BDH), 34.9% water, 0.1% acetic acid, pH 5.6, as solvent. Absorbance was monitored with an on-line spectrophotometer at 280 nm linked to an integrator (Spectraphysics, Mountain View, CA, USA, model SP 4270). The purity of each leukotriene was confirmed before challenge by its elution as a single peak at its retention time of 12.5±0.2 mins (LTC_4) and 23±0.1 min (LTE_4) (mean±SEM, n=15) in this solvent system. The concentration of each leukotriene solution was assessed by ultraviolet scanning at 280 nm, assuming an extinction coefficient of 40,000 cm^{-1}·M^{-1}, and dilutions of each leukotriene were prepared in PBS.

For LTC_4 and LTE_4 challenges, each subject inhaled geometrically increasing concentrations starting at 4×10^{-8} M and 4×10^{-7} M for LTC_4 and LTE_4, respectively, to a maximal concentration of 1×10^{-5} M and 1×10^{-4} M for LTC_4 and LTE_4, respectively. Five sGaw measurements were made at each time-point, namely at 2 and 5 min, and then at 5 min intervals for 15 min. The dose response curve for leukotrienes was constructed from the lowest mean value of sGaw after each inhaled dose. If a 35% decrease in sGaw was not achieved, the concentration of leukotriene in the nebulizer was increased by threefold and the protocol was repeated.

Lysine-aspirin inhalation challenge

Lysine-aspirin inhalation challenge was performed using the method of SCHMITZ-SCHUMANN *et al.* [10]. Lysine-aspirin (Synthelabopharma, Lausanne, Switzerland) was used as a powder containing 900 mg lysine acetylsalicylate with 100 mg glycine. The powder was diluted in 5 ml of water to produce a solution, 180 mg·ml^{-1} (0.55 mol·l^{-1}) lysine acetylsalicylate, which is equivalent to 100 mg·ml^{-1} acetylsalicylic acid. This solution was diluted in 0.9% sodium chloride to produce increasing doubling concentrations ranging 1.25–25 mg·ml^{-1} (3.8–0.076 mol·l^{-1}). One millilitre of lysine-aspirin solution was placed in a Heyer nebulizer driven by compressed air (output 8 l·min^{-1}), which generates an aerosol with a mass median particle diameter of 5 μm. Subjects inhaled the aerosol solution *via* a mouthpiece during normal tidal breathing. Measurements of airway response were made using a spirometer (Micromedical Ltd) and the subjects were studied if baseline FEV_1 was greater than 65% predicted. If the change in FEV_1 was less than 10% after inhalation of normal saline, challenge with lysine-aspirin was performed. Three measurements of FEV_1 were made at 15 and 30 min following each dose of lysine-aspirin, and the maximal reading was recorded. If the fall in FEV_1 was <10%, a doubling concentration of lysine-aspirin was inhaled and the protocol repeated until there was a >15% fall in FEV_1. Measurements of airway response were continued for up to 4 h following a positive reaction.

Data analysis

Airways responsiveness to each agonist was determined by the cumulative dose of agonist required to induce a 35% fall in sGaw (PD_{35}) as determined by linear interpolation from the log dose response curve. The PD_{35}sGaw LTE_4 in aspirin-tolerant asthmatic subjects Nos. 5 and 7 was extrapolated from the log dose response curve, since there was only 31 and 30% fall in sGaw, respectively, following inhalation of the highest dose of LTE_4. All values were log transformed for analysis. Results were considered to be significantly different if p=0.05 or less. Differences in airway response to bronchoconstrictor agonists between groups of asthmatic subjects were analysed using t-test for independent observations. The relative response of inhaled leukotriene to histamine was determined by the ratio of PD_{35}sGaw histamine to PD_{35}sGaw LTC_4 or PD_{35}sGaw LTE_4. The time course of recovery following LTC_4 or LTE_4 inhalation was not analysed, since inhaled bronchodilator therapy was required by some subjects following maximal bronchoconstriction.

Results

The concentration of lysine-aspirin administered in aspirin-sensitive subjects was 2.7±0.6 mg·ml^{-1} (mean±SEM,

Table 2. – Airway response to histamine, LTC_4 and LTE_4

Subject No.	PD_{35}sGaw His nmol	PD_{35}sGaw LTC_4 nmol	PD_{35}sGaw LTE_4 nmol
Aspirin-sensitive asthmatic subjects			
1	25	0.032	0.55
2	300	0.13	2.2
3	110	0.035	0.002
4	900	0.3	1.6
5	170	0.12	0.16
6	40	0.016	0.3
7	38	0.027	0.24
GM	110	0.06	0.24*
Control asthmatic subjects			
1	360	0.46	1.0
2	8	0.4	0.2
3	480	0.005	0.85
4	360	0.018	0.13
5	1800	0.04	28.0
6	320	0.48	8.0
7	480	0.17	20.0
8	70	0.42	7.5
9	7	0.004	8.0
10	50	0.15	2.1
11	190	0.065	3.8
12	240	0.69	5.0
13	100	0.055	0.5
GM	140	0.09	2.45

PD_{35}sGaw: cumulative dose of agonist producing a 35% fall in specific airway conductance; His: histamine; LTC_4: leukotriene C_4; LTE_4: leukotriene E_4; GM: geometric mean. *: p=0.02 *vs* control asthmatic subjects.

n=7). Control asthmatic subjects inhaled 25 mg·ml^{-1} lysine-aspirin with no effect. There was no correlation between the dose of lysine-aspirin inhaled in aspirin-sensitive asthmatic subjects and the airway response to LTC_4 and LTE_4 (r=0.338, p=0.51; r=0.31, p=0.53, respectively).

Airway response to histamine, LTC_4 and LTE_4

The PD_{35}sGaw histamine, PD_{35}sGaw LTC_4 and PD_{35}sGaw LTE_4 in individual subjects is shown in table 2. There was no significant difference in PD_{35}sGaw histamine between aspirin-sensitive and the control asthmatic subjects.

Following LTC_4 inhalation, maximal bronchoconstriction occurred within 2–5 min and did not differ between aspirin-sensitive and control asthmatic subjects. The PD_{35}sGaw LTC_4 in aspirin-sensitive asthmatic subjects was 0.06 nmol (GM, range 0.032–0.3 nmol), which was not significantly different from the PD_{35}sGaw LTC_4 in the control asthmatic subjects, which was 0.09 nmol (GM, range 0.004–0.69 nmol) (p=0.5). In the control asthmatic subjects there was no significant difference in PD_{35}sGaw LTC_4 between atopic or non-atopic asthmatic subjects (p=0.9).

Following LTE_4 inhalation, maximal bronchoconstriction occurred within 5–10 min and did not differ between aspirin-sensitive and control asthmatic subjects. The GM $PD_{35}LTE_4$ was 0.24 nmol (GM, range 0.002–2.2 nmol) and 2.45 nmol (GM, range 0.13–28.0 nmol) in aspirin-sensitive and control asthmatic subjects, respectively, (p=0.02). The airways of aspirin-sensitive asthmatic subjects were significantly (10.2 fold) more responsive to LTE_4 than control asthmatic subjects. In aspirin-sensitive subject No. 3, there was a 60% fall in sGaw following inhalation of the first dose of LTE_4. There was no significant difference in GM PD_{35}sGaw LTE_4 between the atopic and non-atopic control asthmatic subjects (p=0.6).

Table 3. – Relative response of LTC_4 or LTE_4 to histamine

Subject No.	PD_{35}sGaw His / PD_{35}sGaw LTC_4	PD_{35}sGaw His / PD_{35}sGaw LTE_4
Aspirin-sensitive asthmatic subjects		
1	781	45
2	2307	136
3	3142	55000
4	3000	562
5	1416	1062
6	2500	133
7	1407	158
GM	1862	457*
Control asthmatic subjects		
1	782	360
2	20	40
3	96000	564
4	20000	2769
5	45000	64
6	666	40
7	2823	24
8	166	9
9	1750	1
10	333	24
11	2923	50
12	347	48
13	1818	200
GM	1584	58

For abbreviations see legend to table 2. *: p=0.05 *vs* control asthmatic subjects.

Responsiveness of the airways to LTC_4 and LTE_4 relative to that of histamine

The responsiveness of the airways to LTC_4 and LTE_4 compared with histamine is shown in table 3. The responsiveness of the airways to LTC_4 relative to histamine was 1,862 (GM, range 781–3,142) and 1,584 (GM, range 20–96,000) in aspirin-sensitive and control asthmatic subjects, respectively, and was not significantly different. There was no significant difference in responsiveness of the airways to LTC_4 relative to histamine between atopic and non-atopic control asthmatic subjects. The responsiveness of the airways to LTE_4 relative to histamine was 457 (GM, range 45–55,000) in aspirin-sensitive subjects, which was significantly different from the control asthmatic subjects (58 GM, range 0.8–2,769) (p=0.05). There was no significant difference between the responsiveness of the airways to LTE_4 compared to histamine between atopic and non-atopic control asthmatic subjects.

Discussion

Aspirin-sensitive asthmatic subjects demonstrate increased airways responsiveness to inhaled LTE_4 but not to LTC_4 or histamine, when compared to asthmatic subjects who are aspirin-tolerant. This study was prompted by the following two observations which we had made previously. Firstly, whilst airways of asthmatic subjects were approximately 14, 15, 6 and 9 fold more responsive to histamine, methacholine, LTC_4 and LTD_4, respectively, airways of subjects with bronchial asthma were 219 fold more responsive to LTE_4 [11]. Thus, there was a substantially augmented level of hyperresponsiveness to LTE_4 in bronchial asthma, which was not observed for the other bronchoconstrictor agents. As the nonspecific airways responsiveness increased, the relative potency of LTE_4 also increased, whereas the potency of LTC_4 and LTD_4 decreased. These results suggest that the mechanism of bronchoconstriction induced by LTE_4 may be distinct from that produced by LTC_4 or LTD_4 in subjects with asthma. We suggested that this may reflect leukotriene subtype receptor heterogeneity in asthmatic airways. The difference in PD_{35}sGaw LTE_4 in control asthmatic subjects compared to that of a prior study [11] illustrates the wide range of airway response to LTE_4 which is observed in asthmatic subjects. This occurs despite random selection of subjects and good reproducibility of the leukotriene challenges, as observed from prior studies. For this reason, the airway response of LTE_4 relative to histamine was determined.

The second observation was the finding that the airways of patients with aspirin-induced asthma were significantly more responsive to LTE_4 than asthmatic subjects who were tolerant to aspirin [6]. We reasoned that, if there is an abnormal responsiveness to LTE_4 in asthma, which is not observed for LTC_4 and LTD_4, we may find a disproportionate increase in LTE_4 responsiveness in aspirin-sensitive asthmatic subjects, which is not seen for LTC_4 or LTD_4.

The present study was conducted in Davos, Switzerland, at altitude (1,560 m above sea level), whereas the previous study was performed in London. Thus, the control asthmatic subjects come from a different population and are, therefore, not directly comparable. It is important to note that one of the reasons why asthmatic patients are sent to Davos is because they benefit from the change in environment. Many of these individuals spend at least 6 weeks in Davos, and lung function improves and stabilizes within the first week. Our patients were studied when they were stable. It is likely that the differences observed in LTC_4 and LTE_4 ratio between the patients in Davos and the patients in London [11] is explained by the effects of the environment on airways responsiveness. The present study included aspirin-sensitive and non-aspirin-sensitive patients who had been in Davos for a similar period of time, and the results are, therefore, directly comparable. This study emphasizes the importance for a proper control group for this type of study.

Our results demonstrate that the increased responsiveness seen in aspirin-sensitive asthmatic subjects to LTE_4 is not observed for LTC_4. Thus, the recognition mechanisms for LTC_4 and LTE_4 in the airways of patients with aspirin sensitivity may differ. The finding of enhanced airways response to LTE_4 in aspirin-sensitive asthma is consistent with the findings of ARM *et al.* [6], who demonstrated that aspirin-sensitive asthmatic subjects were approximately 13 fold more responsive to LTE_4 compared to control asthmatic individuals.

We have used specific airways conductance as a measure of large airways function, as previous work has suggested that asthmatic subjects demonstrate a greater response to LTE_4 in the central airways [12]. Apart from the possibility of leukotriene subtype receptor heterogeneity, our results may be explained by the possibility that LTC_4 and LTE_4 had a different site of deposition, or that there was a difference between asthmatic and normal subjects in the rate of metabolism with LTC_4 and LTE_4.

It seems unlikely that differential deposition was the explanation for our data, although this cannot be excluded. The leukotrienes were prepared in an identical manner by an independent investigator and the inhalation challenges were performed in random order and blind. Furthermore, each volunteer was subjected to each of the three challenges. Methods of nebulization and inhalation were identical for all doses of leukotrienes in all subjects.

Because there is bioconversion of LTC_4 to LTD_4 to LTE_4, a possible explanation for our observations may be that the metabolism of LTC_4 to LTD_4 to LTE_4 occurred more rapidly in aspirin-sensitive individuals than in asthmatic subjects who were aspirin-tolerant. There are no data on the rate of metabolism of LTC_4 in aspirin-sensitive subjects, although work is in progress to evaluate this question.

The most interesting possibility for the difference between LTC_4 and LTE_4 is that there are different sulphidopeptide leukotriene recognition mechanisms, and that there may be differential expression of these receptors between the two groups of asthmatic subjects studied. If LTE_4 had a distinct recognition unit that was expressed relatively more than the receptor for LTC_4 in airways of aspirin-sensitive individuals, then the different relative responsiveness of LTC_4 and LTE_4 to the reference agonist would be explained. There is significant evidence in guinea-pigs to support the suggestion that separate receptors exist [13–17]. However, in man, there is no pharmacological or radioligand binding data to support the view of receptor heterogeneity. A previous study, conducted in the presence of bioconversion inhibitors on intralobar airways isolated in human subjects undergoing surgery for carcinoma of the bronchus, has revealed no evidence for multiple leukotriene receptors [18]. However, airways from asthmatic subjects were not studied, and the influence of underlying airway inflammation on receptor expression is unknown.

Apart from differences in the response to inhaled leukotrienes in aspirin sensitivity, there appear to be selective alterations in responsiveness to prostaglandins in aspirin-induced asthma. SZCZEKLIK *et al.* [19] investigated the airway response to $PGF_{2\alpha}$ in aspirin-sensitive, atopic and non-atopic asthmatic subjects [19]. Atopic subjects were reactive to low-doses of histamine and $PGF_{2\alpha}$. Aspirin-sensitive asthmatic subjects had similar airways responses to histamine, but tolerated higher doses of $PGF_{2\alpha}$. In patients with intrinsic asthma, even larger doses of histamine and $PGF_{2\alpha}$ were necessary to induce bronchoconstriction. The response to PGE_2 was similar in all three groups of asthmatic subjects, although in aspirin-sensitive asthmatic individuals, peak bronchodilatation occurred at the end of PGE_2 inhalation, unlike the response in atopic and intrinsic asthmatic subjects, in whom bronchodilatation occurred up to 30 min later.

The finding that the airways of patients with aspirin sensitivity have a significantly augmented responsiveness to LTE_4 compared to asthmatic subjects who are tolerant of aspirin, suggests that sulphidopeptide leukotriene antagonists, with a specificity for LTE_4, may be particularly beneficial to asthmatic subjects with aspirin sensitivity. In this respect, the sulphidopeptide leukotriene receptor antagonist SK&F 104353 has already been shown to significantly attenuate aspirin-induced bronchospasm [9].

References

1. Samuelsson B. – Leukotrienes: mediators of hypersensitivity reactions and inflammation. *Science* 1983; 220: 568–575.
2. Bach MK, Brashler J, Morton D. – Solubilization and characterization of the leukotriene C_4 synthetase of rat basophil leukaemia cells. A novel particulate glutathione-S-transferase. *Arch Biochem* 1984; 230: 455–465.

3. Lewis RA, Drazen JM, Austen KF, Clarke DA, Corey EJ. – Identification of the C(6)-S-conjugate of leukotriene A with cysteine as a naturally occurring slow reacting substance of anaphylaxis (SRS-A). Importance of the 11-cis-geometry for biological activity. *Biochem Biophys Res Commun* 1980; 96: 271–277.
4. Morris HR, Taylor GW, Piper PJ, Tippins JR. – Structure of slow-reacting substance of anaphylaxis from guinea-pig lung. *Nature* 1980; 285: 104–105.
5. Drazen JM, Austen KF, Lewis RA, *et al.* – Comparative airway and vascular activity of leukotriene C-1 and D *in vivo* and *in vitro*. *Proc Natl Acad Sci USA* 1980; 77: 4354–4358.
6. Arm JP, O'Hickey SP, Spur BW, Lee TH. – Airway responsiveness to histamine and leukotriene E_4 in subjects with aspirin-induced asthma. *Am Rev Respir Dis* 1989; 140: 148–153.
7. Christie PE, Tagari P, Ford-Hutchinson AW, *et al.* – Urinary leukotriene E_4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis* 1991; 143: 1025–1029.
8. Knapp HR, Sladek K, Fitzgerald GA. – Increased excretion of leukotriene E_4 during aspirin-induced asthma. *J Lab Clin Med* 1992; 119: 48–51.
9. Christie PE, Smith CM, Lee TH. – The potent and selective sulphidopeptide leukotriene antagonist SK&F 104353, inhibits aspirin-induced asthma. *Am Rev Respir Dis* 1991; 144: 957–958.
10. Schmitz-Schumann M, Schaub E, Virchow C. – Inhalative Povokation mit Lysin-Azetylsalizylsaure beim Analgetika-Asthma-Syndrom. *Prax Klin Pneumol* 1982; 36: 17–21.
11. Arm JP, O'Hickey SP, Hawksworth R, *et al.* – Asthmatic airways have a disproportionate hyperresponsiveness to LTE_4, as compared to normal airways, but not to LTC_4, LTD_4, methacholine and histamine. *Am Rev Respir Dis* 1990; 142: 1112–1118.
12. Davidson AB, Lee TH, Scanlon PD, *et al.* – Bronchoconstrictor effects of leukotriene E_4 in normal and asthmatic subjects. *Am Rev Respir Dis* 1987; 135: 333–337.
13. Drazen JM, Lewis RA, Austen KF, Corey EJ. – Pulmonary pharmacology of the SRS-A leukotrienes. *In*: Leukotrienes and Prostacyclin. Berti F, Folco G, Velo GP, eds. New York, Plenum Press, 1983; pp. 125–134.
14. Krell RD, Tsai BS, Berdoulay A, Barne M, Giles RE. – Heterogeneity of leukotriene receptors in guinea-pig trachea. *Prostaglandins* 1983; 25: 171–178.
15. Hogaboom GK, Mong S, Wu H-L, Crooke ST. – Peptidoleukotrienes: distinct receptors for leukotrienes C_4 and D_4 in the guinea-pig lung. *Biochem Biophys Res Commun* 1983; 116: 113–143.
16. Pong SS, DeHaven R. – Characterization of a leukotriene D_4 receptor in guinea-pig lung. *Proc Natl Acad Sci* 1983; 80: 7415–7419.
17. Aharony D, Catanese CA, Falcone R. – Kinetic and pharmacologic analysis of [^{3}H]leukotriene E_4 binding to receptors on guinea-pig lung membranes: evidence for selective binding to a subset of leukotriene D_4 receptors. *J Pharmacol Exp Ther* 1989; 248: 581–588.
18. Buckner CK, Krell RD, Lavaruso RB, Coursin DB, Bernstein PR, Will JA. – Pharmacological evidence that human intralobar airways do not contain different receptors that mediate contractions to leukotriene C_4 and D_4. *J Pharmacol Exp Ther* 1986; 237: 558–562.
19. Szczeklik A, Nizankowska E, Nizankowska R. – Bronchial reactivity to prostaglandins $F_{2\alpha}$, E_2, and histamine in different types of asthma. *Respiration* 1977; 34: 323–331.