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Effects of a thromboxane-receptor antagonist, BAY u 3405, on prostaglandin D_2- and exercise-induced bronchoconstriction

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In the pathogenesis of exercise-induced bronchoconstriction (EIB), prostaglandin D_2 (PGD_2) may play a role as a newly generated, mast cell-derived mediator. As the bronchoconstrictor effects of PGD_2 are predominantly mediated via stimulation of thromboxane receptors in the lung, we studied a novel, orally effective, thromboxane-receptor antagonist, BAY u 3405, on EIB in 12 male subjects with mild asthma. On 4 study days, we determined, in a randomized, double-blind, placebo-controlled, crossover fashion, the effects of 20 mg of BAY u 3405 administered orally 1 hour before PGD_2 and exercise challenges, respectively. Increasing dosages of PGD_2 were inhaled to establish dose-response curves that allowed determination of the provocative concentration necessary to decrease FEV_1 by at least 20% (PC_{20}) and to increase specific airway resistance (SR_{aw}) by 100% (PC_{100}). EIB was measured as a maximal fall/increase in postexertional FEV_1/SR_{aw} after bicycle exercise and cold-air breathing. Prechallenge lung-function values were similar on all four occasions. BAY u 3405 did not elicit any effect on resting bronchial tone. After placebo, the geometric means (SD) of PC_{20} and PC_{100} were 0.0380 (2.6) and 0.0266 (2.4) mg/ml, increasing to 0.554 (5.9) and 0.143 (8.1) mg/ml after BAY u 3405 (p = 0.0002). Mean (SD) maximal postexertional decrease in FEV_1 and increase in SR_{aw} after placebo was 29.4% (16.4%) and 280% (135%), and after BAY u 3405, 31.4% (18.1%) and 379% (281%) (not significant). No clinically relevant BAY u 3405-related side effects were observed. From these results we conclude that BAY u 3405 is highly effective in attenuating PGD_2-induced bronchoconstriction. However, BAY u 3405 does not modulate EIB, suggesting that the mast cell-derived mediator, PGD_2, does not play an important role in the pathogenesis of exercise-induced asthma. (J Allergy Clin Immunol 1992;89:1119-26.)

Key words: *BAY u 3405, thromboxane-receptor antagonist, PGD_2 challenge, exercise challenge, patients with asthma*

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Airway hyperresponsiveness to a variety of stimuli is one of the characteristic features of BA, and PGD_2 has been demonstrated to induce bronchoconstriction in subjects with asthma.[1] PGD_2 is an important cyclooxygenase metabolite of arachidonic acid in the mast cell,[2] and substantially elevated levels of PGD_2 in the BALF of patients with mild asthma have been reported.[3, 4]

The bronchoconstrictor effect of PGD_2 is predominantly mediated via thromboxane receptors in the lung,[5] and BAY u 3405 is a novel, selective thromboxane A_2-receptor antagonist that belongs to a group of cycloalkanoindolesulphonamides.[6] One purpose of our study was therefore to investigate the ability of BAY u 3405 to attenuate PGD_2-induced bronchoconstriction in subjects with BA.

Exercise is a naturally occurring stimulus that often provokes bronchoconstriction in patients with BA, referred to as EIA. EIA is influenced by the temperature and humidity of the inspired air,[7-15] the osmolarity of the epithelial lining fluid,[8, 9] and changes of the blood flow in the microvasculature of the tracheobronchial tree.[13, 15] These events are believed to release mediators with the development of airway narrowing.[16-20] The nature of these constrictor mediators is unknown, but PGD_2 may play a role in so far as intrabronchial mast cells are involved in the pathogenesis of EIA.[21, 22] The second purpose of our study was to investigate the effect of the thromboxane-receptor antagonist, BAY u 3405, on EIB. With this approach, we were able to compare, on an individual basis, the ability of BAY u 3405 to protect specifically against PGD_2-induced airway narrowing with its effect on EIB.

Abbreviations used

BA:	Bronchial asthma
PGD_2:	Prostaglandin D_2
EIA:	Exercise-induced asthma
EIB:	Exercise-induced bronchoconstriction
PC:	Provocative concentration
PC_{20}:	Provocative concentration necessary to decrease FEV_1 by 20%
SR_{aw}:	Specific airway resistance
PC_{100}:	Provocative concentration necessary to increase SR_{aw} by 100%
SD:	Standard deviation
BAL:	Bronchoalveolar lavage
BALF:	Bronchoalveolar lavage fluid
LTB_4, LTC_4, LTD_4, LTE_4:	Leukotrienes B_4, C_4, D_4, and E_4

MATERIAL AND METHODS

Patients

We investigated 12 male subjects with mild to moderate BA recruited from our outpatient pulmonary clinic. Individual characteristics of the subjects are presented in Table I. All subjects fulfilled the diagnostic criteria of BA proposed by the American Thoracic Society.[23] Mean (SD) FEV_1 was 90.1% (12%) predicted. In all subjects the concentration of inhaled histamine necessary to induce PC_{20} was ≤ 2.0 mg/ml, compatible with airway hyperresponsiveness. All subjects had a history of EIB, documented by a fall in FEV_1 of at least 20% after exercise and cold-air breathing. In all subjects airway hyperresponsiveness to inhaled PGD_2 was proven and defined as a PGD_2-induced fall in FEV_1 of at least 20% at a PGD_2 concentration of <0.5 mg/ml. All except one subject had documented diurnal variations in peak expiratory flow rates >20%. Ten subjects were judged atopic on the basis of positive skin tests to common allergens. All subjects were nonsmokers. Seven subjects were receiving medication. Details are presented in Table I. In all subjects inhaled sympathomimetic agents could be withheld for at least 8 hours before the study sessions. Inhaled corticosteroids were kept constant during the study. The subjects were informed about the aim of the study and gave written consent. The approval of an ethical committee was obtained.

Methods

Lung function measurements. Airway resistance was determined during quiet breathing, and thoracic gas volume was measured at functional residual capacity with a constant-volume body plethysmograph (Body-Test; E. Jaeger, Würzburg, Germany) connected to a computer (PDP II/04; Digital Equipment Corp., Maynard, Mass.). Airway resistance was multiplied by thoracic gas volume for the calculation of SR_{aw}. Spirometry was performed with a pneumotachograph whose differential pressure signal was electronically integrated to elicit volume. Normal values were taken from the European Community for Coal and Steel.[24]

Histamine- and PGD_2-inhalation challenges. Bronchial challenges with histamine and PGD_2 were performed according to the method of Chai et al.[25] with a DeVilbiss nebulizer (No. 646, DeVilbiss Co., Somerset, Pa.) triggered by a breath-synchronized solenoid valve that remained open for 0.6 sec. Mean nebulizer output per actuation was 0.016 ml at 20 psi. Increasing (0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1, 2, 4, and 8 mg/ml) concentrations of histamine diphosphate (Sigma Chemie, Taufkirchen, Germany) were prepared daily with a phosphate buffer as diluent. PGD_2 was purchased from Salford Ultrafine Chemicals and Research Ltd., Manchester, England. The following concentrations

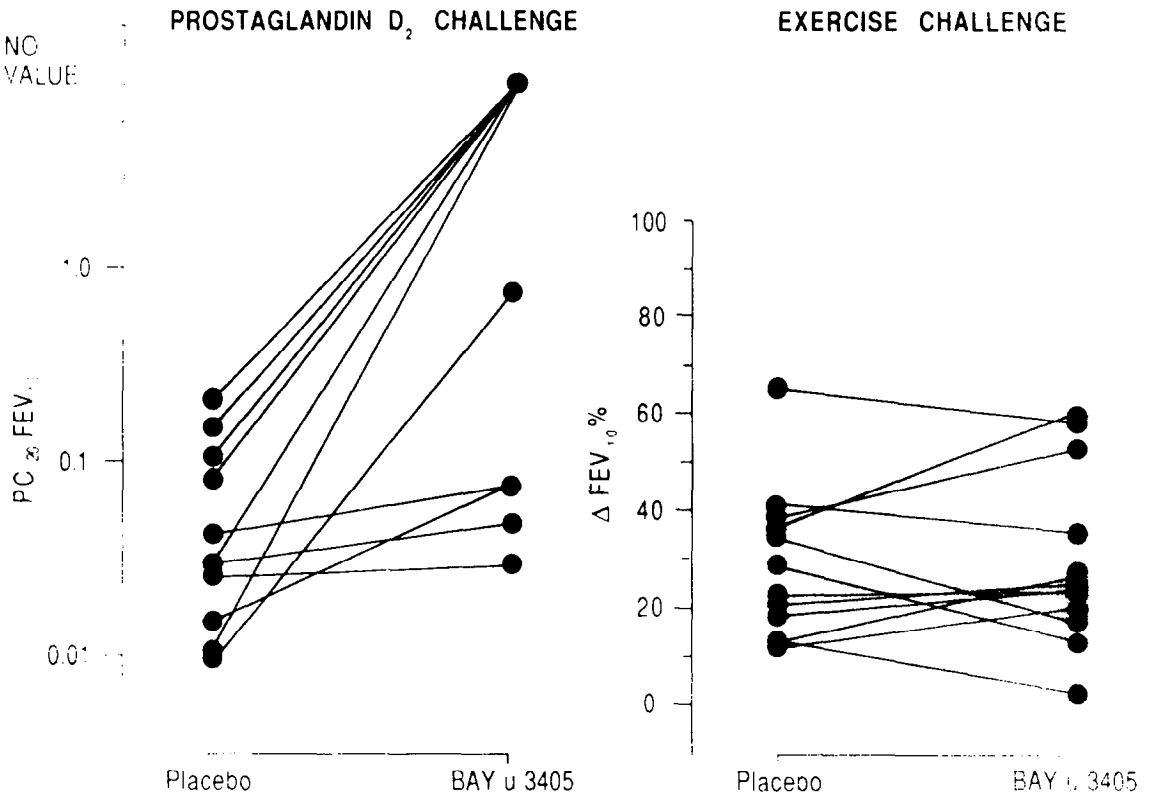

FIG. 1. Individual data of the effects of BAY u 3405 and placebo treatment on the PC of PGD_2, necessary to reach PC_{20} and maximum percent postexertional change of FEV_1. "No value" indicates that PC_{20} was at least higher than 1 mg/ml after inhaling PGD_2 (see Table II).

of PGD_2 were prepared with a phosphate buffer as diluent: 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1, and 2 mg/ml.

The subjects were instructed to take five breaths starting from functional residual capacity and to inhale to total lung capacity at a constant inspiratory flow of about 2 L/sec. After baseline values and the airway response to the diluent were measured, lung function was determined 1 and 3 minutes after the inhalation of increasing concentrations of histamine or PGD_2 solutions. All measurements were performed in duplicate, and the average was taken for SR_{aw} and the best value for FEV_1. Each provocation step lasted 5 minutes. Dose-response curves were constructed by plotting SR_{aw} and FEV_1 against the logarithms of histamine and PGD_2 concentrations. The PC of the inhalant was defined as the concentration necessary to increase SR_{aw} by 100% compared with that of the response to the diluent (PC_{100}) or to decrease FEV_1 by 20% (PC_{20}). With this method, hyperresponsiveness was defined as a PC value <8 mg/ml for histamine and a PC value <0.5 mg/ml for PGD_2.

Cold-air breathing during exercise. Cold air was produced by passing dried room air through a heat exchanger. Inspiratory and expiratory temperatures were measured by two thermocouples situated within the respective ports of a two-way valve (Hans Rudolph, Inc., Kansas City, Mo.). Expired air was conducted through a heated pneumotachograph (Fleisch No. 4), and airflow was integrated electronically to elicit minute volume. Respiratory heat exchange was calculated according to the formula by Deal et al.[24]

Exercise was performed on a bicycle ergometer for 6 minutes. Lung function was measured before and 3, 8, 15, and 30 minutes after the end of cold-air breathing. The response of the airways to the exercise test was assessed by comparing the lowest and highest postexertional values of FEV_1 and SR_{aw} with the respective prechallenge values.

Study design. Each subject was studied within a period of 2 to 15 weeks. Clinical investigation, inhalation challenges with histamine and PGD_2, and an exercise test were performed in a prestudy period. On 4 study days, each separated by at least 48 hours, PGD_2 challenges and exercise tests were performed after placebo and BAY u 3405 administration in a randomized, crossover, and double-blind fashion. After 30 minutes of rest, lung function measurements were performed (baseline values). The subjects then received their study medication, either placebo or 20 mg of BAY u 3405 (one tablet), and lung function was measured 1 hour after administration (prechallenge values), the time when maximal BAY u 3405 plasma concentrations were expected.[26] Finally, PGD_2-inhalation challenge or exercise tests were performed.

Data evaluation and statistics. Arithmetic mean value and SD were computed for lung-function values, the experimental conditions during exercise, and the postexer-

TABLE I. Individual characteristics of subjects

Subject	Sex	Age (yr)	Height (cm)	Weight (kg)	Atopy (±)	VC (L_{BTPS})	FEV_1 (% pred)
1	M	22	183	85	+	5.71	109.7
2	M	21	183	80	+	6.92	103.7
3	M	48	178	76	−	5.24	87.5
4	M	19	177	80	+	4.96	84.1
5	M	20	180	80	+	5.65	103.8
6	M	24	182	71	+	5.07	97.4
7	M	21	168	68	+	4.45	80.5
8	M	38	176	73	+	4.49	88.4
9	M	19	178	80	+	5.08	83.9
10	M	21	180	75	−	5.60	95.4
11	M	20	173	58	+	5.12	74.2
12	M	26	186	95	+	4.58	72.2

VC, Vital capacity; *PEFR*, peak expiratory flow rate; *min*, minimum; *max*, maximum; *S*, salbutanol; *BDP*, beclomethasone, *BUD*, budesonide; *F*, fenoterol; *ND*, not determined.

*Peak expiratory flow rates measured early morning (min) and maximum daytime (max) within 2 weeks before the study.

†Airway responsiveness was assessed with inhaled histamine.

‡Inhaled bronchodilators: F and S, daily dose in micrograms; inhaled corticosteroids: BDP and BUD, daily dose in micrograms.

tional airway response. For the provocative concentrations of histamine and PGD_2, geometric mean values were calculated, and their variability was expressed as geometric SD (variability factor). In the subjects in which BAY u 3405 pretreatment resulted in a marked protective effect, a PC_{20} or PC_{100} could not be obtained without inhaling undesirably high concentrations of PGD_2. Therefore, a PC_{20}-PC_{100} of 2 mg/ml was assumed to allow for statistical evaluation. Data were compared with Student's paired *t* test. Significance was assumed for $p < 0.05$.

RESULTS

Prechallenge lung-function values

BAY u 3405 did not demonstrate any effects on resting bronchial tone. One hour after the administration of BAY u 3405 and placebo, the mean (SD) values of FEV_1 were 3.85 (0.50) L and 3.74 (0.48) L, respectively. Mean (SD) values of prechallenge SR_{aw} and FEV_1 of the two PGD_2 challenge tests were not significantly different (Table II). SR_{aw} and FEV_1 measured before the two exercise tests did not demonstrate significant differences (Table III). Prechallenge SR_{aw} and FEV_1 were not different between the pair of challenges.

PGD_2-inhalation challenge

Individual data for PC_{100} (PGD_2) and PC_{20} (PGD_2) are presented in Table II. After placebo administration, geometric mean (SD) of PC_{100} and PC_{20} were 0.0266 (2.4) mg/ml and 0.0380 (2.6) mg/ml, respectively. After BAY u 3405 pretreatment, inhalation of the highest PGD_2 concentration used to establish the dose-response curve (2 mg/ml) was not effective to increase SR_{aw} by 100% in three subjects nor to decrease FEV_1 by 20% in six subjects. We therefore assumed that in these subjects the provocative concentration of PGD_2 was 2 mg/ml. Then, posttreatment geometric mean (SD) of PC_{100} was 0.143 (8.1) mg/ml and PC_{20} was 0.554 (5.9) mg/ml. The thromboxane-receptor antagonist, BAY u 3405, therefore significantly protects against the bronchoconstriction induced by inhaled PGD_2 ($p = 0.0002$) (Fig. 1).

Cold-air breathing during exercise

Exercise ventilation, inspired temperature, and respiratory heat exchange were not significantly different after placebo and BAY u 3405 pretreatment. Mean (SD) values were 56.2 (9.6) L/min, −15.8 (0.72)° C, and 1.44 (0.24) kcal/min, and 56.0 (10.5) L/min, −15.9 (0.79)° C, and 1.45 (0.27) kcal/min, respectively.

Individual data for the maximum increase in SR_{aw} and the maximum decrease in FEV_1 observed within 30 minutes after exercise and cold-air breathing are presented in Table III.

After placebo treatment, mean (SD) SR_{aw} increased from 9.4 (3.4) to 36.5 (19.8) cm H_2O per second corresponding to a mean (SD) percentage maximal change of +280% (135%). Mean (SD) FEV_1 decreased from 3.8 (0.5) to 2.7 (0.7) L corresponding to a mean (SD) percentage maximal change of −29.4% (16.4%).

After BAY u 3405 treatment, mean (SD) SR_{aw} in-

PEFR* (L/min)		PC_{20}	Therapy‡
Min	Max	(mg/ml)†	(μg)
500	600	0.548	S_{800}/BDP_{1000}
460	560	0.216	S_{200}
325	425	2.0	S_{800}/BUD_{1600}
440	540	0.185	S_{200}/BDP_{800}
532	610	0.047	—
ND	ND	1.07	—
350	517	0.05	S_{800}/BDP_{800}
400	600	1.6	—
480	600	<0.1	S_{800}
400	600	0.772	F_{800}/BDP_{1000}
370	500	0.579	—
410	510	0.431	—

creased from 8.6 (2.8) to 40.3 (26.2) cm H_2O per second corresponding to a mean (SD) percentage maximal change of +379% (281%). Mean (SD) FEV_1 decreased from 3.9 (0.4) to 2.7 (0.8) L corresponding to a mean (SD) maximum percent fall of 31.4 (18.1) (Fig. 1). The effects of placebo and BAY u 3405 pretreatment on EIB and cold-air breathing were therefore not significantly different.

The prestudy exercise test performed without premedication and under identical experimental conditions in terms of exercise ventilation, inspired temperature, and respiratory heat exchange induced a mean (SD) maximum increase in SR_{aw} of 275% (180%) and a mean (SD) maximum decrease in FEV_1 of 29.6% (12.3%). These values did not differ significantly between study days.

Side effects

In one subject (No. 1) pretreatment with BAY u 3405 allowed inhalation of 4.0 mg/ml of PGD_2 that was followed by hot flushes, red face, slight fine muscular tremor, and restlessness, but no dyspnea. Blood pressure, pulse rate, and temperature were 120/80 mm Hg, 72 beats/min, and 36.8° C, respectively. The symptoms disappeared within about 2 hours. To avoid similar events that we attributed to the high concentration of PGD_2, the highest inhaled dosage of PGD_2 was limited to 2 mg/ml. With this restriction, we did not observe similar side effects.

In all subjects, PGD_2-induced bronchoconstriction was reversible within about 10 minutes after inhaling one to two puffs of a β_2-adrenoceptor agonist.

DISCUSSION

In this study of 12 subjects with mild to moderate asthma, we found that, compared with placebo, the thromboxane-receptor antagonist, BAY u 3405, shifted the dose-response curve to inhaled PGD_2 14.5-fold to the right. However, the same orally effective dose of 20 mg of BAY u 3405 administered 1 hour before the challenge did not modulate the airway response to cold-air breathing during exercise, suggesting that PGD_2 does not play a significant role in EIA.

PGD_2 is one of the bronchoconstrictor prostanoids released from stimulated human mast cells of atopic subjects with asthma.[27] Recently, Beasley et al.[28] demonstrated that the selective and potent thromboxane-receptor antagonist, GR32191, caused a significant inhibition of PGD_2-induced bronchoconstriction and attenuated the early bronchoconstrictor response to inhaled allergen in atopic subjects with asthma. From these investigations, the authors suggested that prostanoids contribute to the immediate airway narrowing after inhalation of allergen and that this effect is mediated by a thromboxane receptor.

In the present study, we have investigated another orally effective thromboxane-receptor antagonist and demonstrated that 20 mg of BAY u 3405 1 hour before the challenge shifted the PGD_2 concentration-response curve to the right by at least 14-fold compared with that of a tenfold displacement observed 1 hour after oral administration of 80 mg of GR32191.[28] Because the clinical characteristics of the subjects with asthma studied by Beasley et al.[28] and in our study were similar, the thromboxane-receptor antagonist BAY u 3405 is considered to be equally effective in attenuating PGD_2-induced bronchoconstriction.

In many atopic and nonatopic subjects with asthma, exercise is a stimulus followed by transient airflow obstruction. It has been well established that EIA develops in proportion to the respiratory heat loss[15] as well as respiratory water loss,[8, 9] but there is no accepted explanation for coupling the thermic or osmotic events with bronchoconstriction. The role of mediators has been studied in some detail[17-20] without settling the problem. Recently, Pliss et al.[21] studied mediators and cells in the BALF before and after inducing bronchoconstriction by isocapnic hyperventilation. Postchallenge BAL revealed elevated concentrations of LTB_4, $LTC_4/LTD_4/LTE_4$, higher eosinophil and epithelial cell numbers, and a trend toward significant increases in PGD_2 and neutrophils. The authors concluded that airflow obstruction induced by isocapnic hyperventilation is associated with a spectrum of bronchoactive mediators and inflammatory cells. In another recently published study, Broide et al.[22] investigated mast cell-derived mediators (histamine, tryptase, PGD_2, and LTC_4) in BALF sampled before and after EIB. They were unable to demonstrate an ex-

TABLE II. Baseline (base) values and effect of pretreatment with BAY u 3405 and placebo

	BAY u 3405					
	SR_{aw}			FEV_1		
Patient No.	Base	Pre	PC_{100}	Base	Pre	PC_{20}
1	8.6	4.3	0.170	4.9	4.8	>4.0
2	17.0	10.5	0.034	4.2	4.4	0.076
3	8.5	6.3	0.336	3.2	3.4	>1.0
4	9.1	10.8	1.164	3.2	3.2	0.723
5	7.1	6.8	0.023	4.1	4.4	0.047
6	4.7	4.0	0.017	4.3	4.4	>2.0
7	9.1	9.5	0.019	3.1	3.2	0.033
8	3.4	2.9	0.055	3.2	3.2	0.076
9	8.3	7.9	>2.0	4.2	4.0	>2.0
10	4.3	6.7	>2.0	4.1	4.0	>2.0
11	10.1	9.1	0.01	3.3	3.3	>2.0
12	8.9	7.5	>2.0	3.3	3.4	>2.0
Mean	8.3	7.2	0.143*	3.8	3.8	0.554*
SD	3.5	2.6	8.1†	0.6	0.6	5.9†

Values and effect on prechallenge (pre) values for SR_{aw} (cm H_2O per second) and FEV_1 (L_{BTPS}) and the PC of PGD_2 (milligrams per milliliter) necessary to increase SR_{aw} by 100%, PC_{100}, and to decrease FEV_1 by 20%, PC_{20}.
*Geometric mean.
†Geometric standard deviation.

TABLE III. Baseline (base) values and effect of pretreatment with BAY u 3405 and placebo on prechallenge (pre) and maximum/minimum postexertional (post) values for SR_{aw} (cm H_2O per second) and FEV_1 (L_{BTPS})

	BAY u 3405					
	SR_{aw}			FEV_1		
Patient No.	Base	Pre	Post	Base	Pre	Post
1	3.8	4.7	35.4	4.8	4.7	3.6
2	14.9	15.3	35.9	4.0	4.1	3.6
3	9.6	8.6	17.0	3.4	3.4	3.3
4	9.6	10.5	95.8	3.6	3.5	1.4
5	14.4	8.8	71.6	4.4	4.1	1.9
6	5.5	6.5	20.7	4.3	4.4	3.2
7	6.7	6.9	53.6	3.8	3.8	2.8
8	8.5	9.0	22.0	3.4	3.6	2.6
9	9.0	9.4	36.8	4.0	4.1	2.6
10	4.3	4.8	7.9	4.0	4.0	3.3
11	13.8	9.8	64.7	3.6	3.6	1.5
12	10.4	8.4	22.2	3.3	3.5	2.6
Mean	9.2	8.6	40.3	3.9	3.9	2.7
SD	3.8	2.8	26.2	0.5	0.4	0.8

ercise-induced change in the number of BAL mast cells and mast cell-derived mediators, suggesting that the pathogenesis of EIA is independent of mast cells.

In the present study we were unable to modulate EIA by a thromboxane-receptor antagonist that was highly effective in attenuating PGD_2-induced airflow obstruction. This observation does not necessarily mean that mast cells are not involved in the pathogenesis of EIA, because PGD_2 is only one of the mast cell-derived mediators and its interaction with another

Placebo					
SR_{aw}			FEV_1		
Base	Pre	PC_{100}	Base	Pre	PC_{20}
4.7	3.7	0.061	5.0	5.0	0.111
11.8	10.3	0.016	4.3	4.0	0.016
6.2	5.9	0.023	3.2	3.4	0.084
4.6	4.7	0.018	4.0	3.9	<0.015
14.6	12.7	0.017	3.7	3.7	0.03
5.4	5.9	0.016	4.1	3.9	0.022
11.5	13.3	0.016	3.1	2.8	0.022
3.6	3.2	0.036	3.4	3.4	0.040
6.2	8.0	0.017	4.0	3.8	0.021
9.1	6.9	0.09	3.6	3.6	0.146
12.9	9.8	<0.0075	3.0	3.4	0.012
7.5	6.2	0.173	3.4	3.6	0.189
8.2	7.6	0.0266*	3.7	3.7	0.0380*
3.7	3.3	2.4†	0.6	0.5	2.6†

Placebo					
SR_{aw}			FEV_1		
Base	Pre	Post	Base	Pre	Post
6.1	5.9	30.0	4.7	4.6	4.1
16.6	16.5	50.1	4.2	4.1	2.9
11.0	9.2	17.3	3.2	3.4	3.0
9.0	12.4	57.4	4.0	3.1	1.9
14.3	10.1	46.3	4.1	3.8	2.3
5.6	4.3	11.9	4.4	4.4	3.5
8.5	8.1	39.1	3.6	3.6	2.9
6.2	7.4	21.3	3.4	3.4	3.0
11.3	9.6	52.7	4.0	4.2	2.5
7.2	6.8	16.7	3.8	3.9	2.5
10.8	13.5	74.3	3.4	3.5	1.2
9.7	8.8	20.7	3.5	3.4	2.6
9.7	9.4	36.5	3.9	3.8	2.7
3.4	3.4	19.8	0.5	0.5	0.7

newly generated mast cell mediator, LTC_4, has been demonstrated in subjects with asthma.[29]

Our data on the ineffectiveness of BAY u 3405 are in line with that of the study of Finnerty et al.[30] who were also unable to substantiate a protective effect of the thromboxane-receptor antagonist, GR32191, on EIA. Data of our study therefore support an increasing body of evidence that the prostanoid PGD_2, acting via

thromboxane receptors, is not involved in the pathogenesis of EIB.

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