

Role of eicosanoids in airflow obstruction and airway plasma exudation induced by trimellitic anhydride-conjugate in guinea-pigs 3 and 8 weeks after sensitization

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Summary

Trimellitic anhydride (TMA) is a low molecular weight chemical which can cause occupational asthma. We studied the role of eicosanoids in airway responses to TMA at different times after sensitization in actively sensitized guinea-pigs. Sensitization was performed by two intradermal injections of free TMA (0.1 ml of 0.3% TMA in corn oil). At 3 and 8 weeks after sensitization, the guinea-pigs were anaesthetized and challenged with intratracheal instillation of 0.5% TMA conjugated to guinea-pig serum albumin (TMA-GPSA; 50 μ l). Lung resistance (R_L) was measured to assess airflow obstruction, and the tissue content of Evans Blue dye was measured to assess airway plasma exudation. Intratracheal instillation of TMA-GPSA induced a slowly progressing increase in R_L , reaching a peak at approximately 3.5 min after the challenge (6.0 ± 2.0 cm H₂O/ml/s in the 3-week group and 3.8 ± 0.6 in the 8-week group). Pretreatment before challenge with pyrilamine (anti-histamine: 2 mg/kg, intravenously) slowed the onset of the increase in R_L following challenge with TMA-GPSA, and significantly attenuated the peak response. A combination of pyrilamine and ICI-192,605 (thromboxane receptor antagonist; 0.5 mg/kg, intravenously) completely abolished the increase in R_L in both week groups. A combination of pyrilamine and ICI-198,615 (leukotriene C₄/D₄/E₄ receptor antagonist; 0.5 mg/kg, intravenously) did not further attenuate the increase in R_L compared with pretreatment with pyrilamine alone, but the induced Evans Blue dye extravasation was completely inhibited in the 3-week group, whereas a remaining extravasation was observed in the 8-week group. We conclude that the bronchoconstrictor response to TMA-GPSA in actively sensitized guinea-pigs is mediated by histamine and thromboxane A₂ both early and late after sensitization, whereas leukotrienes and histamine partially mediate TMA-induced airway plasma exudation.

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Introduction

Trimellitic anhydride (TMA), a reactive chemical widely used in industry as a curing agent for epoxy resins, may cause occupational asthma in man [1]. Occupational asthma due to TMA is associated with a specific IgE

antibody response in the majority of patients [2]. Recently, an animal model of respiratory allergy to TMA has been developed [3]. After sensitization with TMA given intradermally, guinea-pigs develop specific IgG1 antibodies, and at later time points, when animals are challenged with TMA conjugated to guinea-pig serum albumin (TMA-GPSA), airflow obstruction and airway plasma exudation is induced [4,5]. In this model, airway plasma exudation at different airway levels induced by

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intratracheal challenge with TMA-GPSA, increased at later time points after sensitization (observation up to 8 weeks after sensitization), whereas the induced airflow obstruction subsided over time [5].

In guinea-pigs sensitized to ovalbumin and given intravenous [6] or aerosol challenge [7], leukotrienes (LTs) may be involved in the residual bronchoconstriction not blocked by a histamine H_1 -receptor antagonist. In an animal model of TMA allergy, we have previously reported that pyrilamine, an anti-histamine, significantly attenuates airflow obstruction induced by intratracheal instillation of TMA-GPSA in actively sensitized guinea-pigs [8]. In addition, both OKY-046, a thromboxane (Tx) synthetase inhibitor, and indomethacin significantly reduced the delayed increase in R_L after the challenge. Airway plasma exudation induced by TMA-GPSA was significantly reduced by ICI-198,615, a LT receptor antagonist, but the induced airflow obstruction was not affected [8]. Therefore, our hypothesis is that the remaining bronchoconstriction observed by pretreatment with pyrilamine may be mediated via TxA_2 in this model of TMA induced airway allergy.

The aim of this study was firstly to evaluate whether either LTs or TxA_2 are involved in airway responses to TMA in sensitized guinea-pigs pretreated with pyrilamine, and secondly to investigate whether there are any differences in involvement of eicosanoids in this response at different times after sensitization (3 and 8 weeks).

Materials and methods

Sensitization

Sixty-two male Dunkin Hartley guinea-pigs (250 g) were actively sensitized by two intradermal injections of 0.1 ml of 0.3% (w/v) TMA suspended in corn oil and given 24 h apart. For non-sensitized control animals, 0.1 ml corn oil alone was injected intradermally into 12 guinea-pigs (250 g).

Conjugate

TMA was conjugated to guinea-pig serum albumin (GPSA) using a method described previously [4]. Briefly, four aliquots of 250 mg GPSA were mixed with 50 ml of 9% $NaHCO_3$ on ice and 250 mg of ground TMA dust was slowly added over 10 min. Each aliquot was stirred separately for 1 h. The aliquots were pooled and spun for 10 min at 600 g. The supernatant was separated and dialysed with 0.02 M NH_4HCO_3 (pH 7.4) for 48 h with six changes. This was further dialysed with distilled water for 24 h and lyophilized.

Surgical preparation

Three or 8 weeks after sensitization, the animals were anesthetized with a 3:2 mixture of ketamine (50 mg/ml) and xylazine (20 mg/ml) intramuscularly (1 ml/kg). The guinea-pigs were placed on a heated blanket (Harvard model 50-7061, Harvard Apparatus Ltd, Edenbridge, UK), which maintained body temperature at about 37°C. A polyethylene catheter was inserted into the carotid artery to monitor blood pressure with a pressure transducer (model P23XL, Viggo-Spectramed, Helsingborg, Sweden). The right external jugular vein was cannulated for the administration of drugs and Evans Blue dye. A tracheal cannula (10 mm length and 2.7 mm inner diameter) was inserted into the lumen of the cervical trachea through a tracheostomy, secured with a suture and connected to a constant volume mechanical ventilator (Harvard model 50-1718, Harvard Apparatus Ltd). A tidal volume was 10 ml/kg and a frequency was 60 breaths/min. The ventilatory circuit had a total volume of 18 ml. Airflow was measured with a pneumotachograph (Model FIL; Mercury Electronics Ltd, Glasgow, UK) connected to a transducer (Model FCO44; ± 20 mmH $_2$ O; Funnell Controls Ltd, Bexhill, Sussex, UK). Transpulmonary pressure was measured with a pressure transducer (Model FCO44; ± 1000 mmH $_2$ O; Funnell Controls Ltd), with one side attached to a catheter inserted into the right pleural cavity and the other side connected to a side port of the intratracheal cannula. The signal from the blood pressure transducer was amplified with an analog preamplifier (Kungsbacka mät & reglerteknik AB, Sweden). All signals were digitized with a 12-bit analog digital board (National Instruments, Austin, TX, USA) connected to a Macintosh II computer (Apple computer Inc, Cupertino, Ca, USA) and analysed with a software (LabView, National InstrumentsTM), which was programmed to instantaneously calculate lung resistance (R_L) by the method of von Neergaard and Wirz [9]. Mean blood pressure was also monitored throughout the experiments. All animals were pretreated with suxamethonium (5 mg/kg, intravenously), to avoid artefacts induced by spontaneous breathing.

Protocol

The sensitized guinea-pigs were divided into two groups ($n=31$ in each group) in order to study the role of different mediators in airway responses to TMA 3 and 8 weeks after sensitization with free TMA. Also, the non-sensitized untreated animals were divided into two groups ($n=6$ in each group). Each sensitized group had five sub-groups ($n=6$ or 7 in each sub-group). The first sub-group consisted of the sensitized untreated animals. Other sub-groups of sensitized animals were pretreated with intra-

venous (i.v.) pyrilamine (anti-histamine: 2 mg/kg, i.v.), then 10 min later with ICI-192,605 (thromboxane receptor antagonist; 0.5 mg/kg) [10] or saline (0.9% NaCl), or ICI-198,615 (leukotriene receptor antagonist: 0.55 mg/kg) [11] or its vehicle (8 mg NaOH, 0.275 mg NaH₂PO₄ and 0.2 ml polyethylenglycol 400 in 9.8 ml saline) were given intravenously. Five minutes after pretreatment with these drugs, and 15 min after suxamethonium in untreated animals, Evans blue dye (20 mg/kg) was injected intravenously over 1 min. Another minute later, TMA-GPSA was instilled into the airways. Intratracheal instillation was performed by flushing 50 µl of 0.5% TMA-GPSA with 1 ml of air through a needle, directly into the tracheal lumen via the tracheal cannula. R_L and mean systemic blood pressure was monitored every 15 s over 1 min, and subsequently every 30 s for another 5 min after the instillation of TMA-GPSA.

Determination of airway plasma exudation

Six minutes after instillation of TMA-GPSA, the animals were disconnected from the ventilator and the thoracic cavity was opened. A catheter was inserted into the aorta through the left ventricle, and the animals were perfused with 50 ml of 0.9% NaCl to remove dye within the bronchial circulation. After perfusion through this route, another catheter was inserted into the pulmonary artery, and the pulmonary circulation was then perfused with 20 ml of saline to eliminate dye present in the pulmonary circulation. The trachea and the lungs were dissected out *en bloc*, and the parenchyma carefully scraped off and extraneous tissue removed. The trachea, main bronchi and intrapulmonary airways (IPA) were separated from each other, and intrapulmonary airways were then divided into two lengthwise equal portions, arbitrarily named proximal and distal. All airway tissue were dried, using a freeze dryer (MicroModulyo, Edwards High Vacuum International, West Sussex, UK), for 24 h. All tissue were then weighed dry, and Evans Blue dye was extracted in 2 ml of formamide in a 40°C water bath for 24 h. Absorption at 620 nm was measured in a spectrophotometer (Beckman DB, Ingeniörsfirma Hugo Tillquist, Stockholm, Sweden). The extracted Evans Blue dye was quantified by interpolation on a standard curve of dye concentrations in the range of 0–10 µg/ml, and expressed as ng dye/mg dry tissue. The Evans Blue dye measurement has been previously shown to highly correlate with the extravasation of radiolabelled albumin in guinea-pig airways [12].

Drugs

The following drugs were used: Ketamine hydrochloride (Park-Davis S.A., Barcelona, Spain); Xylazine chloride

(Bayer Sverige AB, Göteborg, Sweden); Suxamethonium chloride (KabiVitum AB, Stockholm, Sweden); Evans Blue dye, Trimellitic anhydride (Aldrich Chemical Co., Milwaukee, USA); Pyrilamine, Guinea-pig serum albumin (Sigma Chemical Co., St Louis, USA); NaOH (EKA, Bohus, Sweden); Polyethylenglycol 400 (KEBO AB, Stockholm). ICI-192,605 and ICI-198,615 were kindly donated by ICI Pharmaceutical Co., USA. The doses of pyrilamine, ICI-192,605 and ICI-198,615 were chosen on the basis of previous experiments [8,10].

Data analysis

Data are reported as mean $\pm$ SEM. To determine the effect of various treatments on the overall response of lung resistance, area under the curves (AUC) was calculated over the 6-min period of R_L measurements. Non-parametric analysis of variance (Kruskal-Wallis method) was used to determine any significant variance among groups. If a significant variance was found, a Mann-Whitney *U*-test was used to test for significant difference between individual groups. A *P*-value less than 0.05 was considered significant. Data were analysed by a Macintosh computer using standard statistical packages (Stat-ViewII).

Results

Baseline

There were no significant differences in body weight, baseline R_L or baseline mean systemic blood pressure between any of the subgroup studied (Table 1). The 3-week group had significantly higher baseline R_L compared with the 8-week group.

Effect of inhibitors of mediators on time course of R_L induced by instilled TMA-GPSA

The effect of various combinations of the antagonists on time course of R_L -change induced by intratracheal instillation of 0.5% TMA-GPSA (50 µl) in the 3 and 8 week group are shown in Figs 1 and 2. Instilled TMA-GPSA induced a slowly progressing increase in R_L , reaching a peak at approximately 3.5 min after the challenge in untreated sensitized guinea-pigs 3 weeks (6.0 ± 2.0 cm H₂O/ml/s) and 8 weeks (3.8 ± 0.6) after sensitization (Figs 1 and 2). When the data were analysed in terms of AUC over 6 min, the AUC was significantly greater in the 3-week group than in the 8-week group, both in sensitized and non-sensitized animals (Fig. 3).

In both the 3- and 8-week groups, pyrilamine (2 mg/kg, i.v.) slowed both the onset of the increase in R_L induced by instilled TMA-GPSA and significantly reduced this re-

Table 1. Body weight, baseline data of lung resistance (R_L), mean systemic blood pressure in the 3 and 8 week group.

Group		Untreated		Pyrilamine (2 mg/kg)			
		Non-sensitized	Sensitized	Saline	ICI-192,605 (0.5 mg/kg)	Vehicle for ICI-198,615	ICI-198,615 (0.55 mg/kg)
3 week	Body weight (g)	413 $\pm$ 22 <i>n</i> = 6	423 $\pm$ 25 <i>n</i> = 6	415 $\pm$ 13 <i>n</i> = 6	420 $\pm$ 8 <i>n</i> = 6	448 $\pm$ 11 <i>n</i> = 6	437 $\pm$ 8 <i>n</i> = 7
	Lung resistance (cmH ₂ O/ml/s)	0.39 $\pm$ 0.04	0.41 $\pm$ 0.02	0.40 $\pm$ 0.03	0.38 $\pm$ 0.02	0.41 $\pm$ 0.02	0.40 $\pm$ 0.02
	Blood pressure (mmHg)	47 $\pm$ 4	49 $\pm$ 3	53 $\pm$ 3	53 $\pm$ 3	47 $\pm$ 4	49 $\pm$ 2
	Body weight (g)	733 $\pm$ 29 <i>n</i> = 7	697 $\pm$ 14 <i>n</i> = 6	733 $\pm$ 16 <i>n</i> = 6	733 $\pm$ 25 <i>n</i> = 6	745 $\pm$ 34 <i>n</i> = 6	732 $\pm$ 35 <i>n</i> = 6
8 week	Lung resistance (cmH ₂ O/ml/s)	0.30 $\pm$ 0.01	0.31 $\pm$ 0.01	0.30 $\pm$ 0.02	0.30 $\pm$ 0.01	0.30 $\pm$ 0.01	0.31 $\pm$ 0.01
	Blood pressure (mmHg)	50 $\pm$ 4	52 $\pm$ 3	54 $\pm$ 3	54 $\pm$ 3	55 $\pm$ 2	54 $\pm$ 4

Values are expressed as mean $\pm$ SEM.

response (Fig. 1). Additional pretreatment with ICI-192,605 (a Tx receptor antagonist; 0.5 mg/kg, i.v.) completely abolished the delayed increase in R_L induced by TMA-GPSA during observation periods (6 min) (Fig. 1). However, ICI-198,615 (a LT receptor antagonist; 0.55 mg/kg, i.v.) did not affect this response, compared with animals pretreated with its vehicle in both week groups (Fig. 2). The level of AUC was significantly smaller in animals pretreated with a combination of pyrilamine and ICI-192,605 than in animals pretreated with pyrilamine only ($P < 0.005$) in both week groups (Fig. 3).

Effect of inhibitors of mediators on extravasation of Evans Blue dye induced by instilled TMA-GPSA

At all airway levels, the amount of Evans Blue dye after instillation with 0.5% TMA-GPSA was significantly higher in sensitized than non-sensitized animals (Fig. 4). Pyrilamine strongly reduced extravasation of Evans Blue dye at all airway levels after instilled TMA-GPSA in sensitized animals. A combination of pyrilamine and ICI-198,615 significantly reduced the extravasation of dye induced by TMA-GPSA in intrapulmonary airways ($P < 0.05$), compared with animals pretreated with its vehicle in the 3-week group, but not in the 8-week group (Fig. 4). ICI-192,605 did not significantly affect the amount of extravasated dye after the challenge in either week groups (Table 2).

Discussion

We have previously demonstrated that in the guinea-pig model of airway allergy to TMA, a histamine H₁-receptor

antagonist strongly antagonizes airflow obstruction after challenge with TMA-GPSA [8,13]. The present study extends these findings, showing an inhibitory response with antihistamine both 3 and 8 weeks after sensitization. The delayed antihistamine-resistant allergen induced airflow obstruction, seen between 3 and 6 min after challenge, may be mediated via synthesis and release of other mediators, such as eicosanoids [13–16]. This hypothesis is further confirmed in the present study, because a combination of pyrilamine and a Tx antagonist (ICI-192,605), but not a LT antagonist (ICI-198,615), abolished the residual airflow obstruction induced by TMA-GPSA both early and late after sensitization.

We have previously found that indomethacin and OKY-046 (a Tx synthetase inhibitor) given alone, significantly attenuate the delayed, but not the immediate increase in R_L in guinea-pigs challenged with TMA-GPSA 3 weeks after sensitization [8]. However, neither BW4AC, a 5-lipoxygenase inhibitor, nor a LT antagonist (ICI-198,615), significantly affect TMA-GPSA induced airflow obstruction [8,13]. Therefore, the present study, taken together with our previous findings, strongly suggest that the release of TxA₂, but not LTs, is involved in airflow obstruction induced by TMA-GPSA in actively sensitized guinea-pigs.

In the guinea-pig model of ovalbumin-induced airway responses, slightly different profiles are sometimes seen. Daffonchio *et al.* [7] found that the remaining airflow obstruction after aerosol challenge with OA in the presence of mepyramine was enhanced by indomethacin (10 mg/kg i.v.). A greater inhibitory effect against OA-

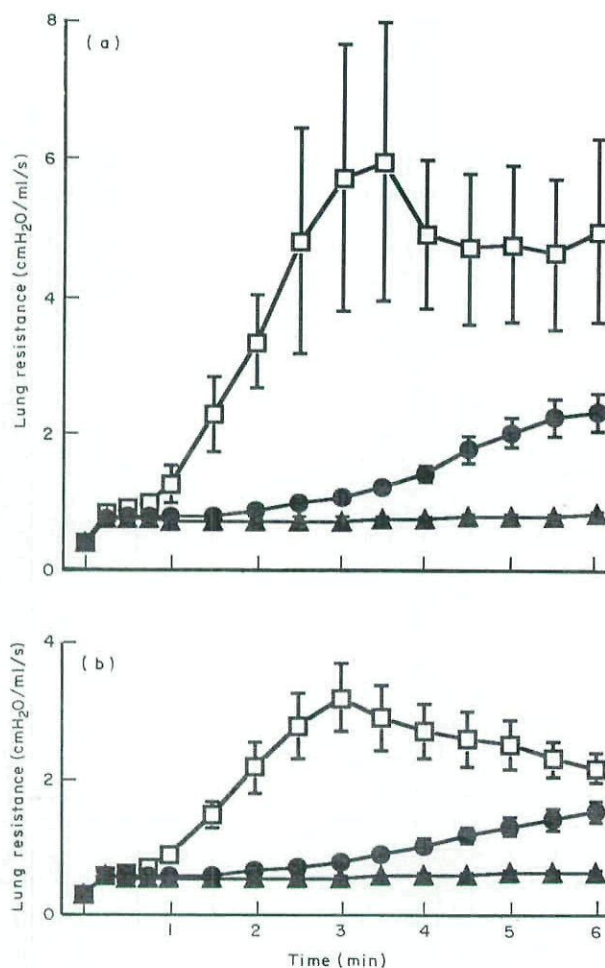


Fig. 1. (a) Effect of a combination of pyrilamine (2 mg/kg, i.v.) and ICI-192,605 (▲, A thromboxane receptor antagonist, 0.5 mg/kg, i.v., $n=6$) or pyrilamine and saline (●, 0.9% NaCl, $n=6$) on time course of lung resistance (R_L) induced by intratracheal instillation of 0.5% TMA-GPSA (50 μ l) in guinea-pigs 3 weeks after sensitization, compared with sensitized untreated animals (□, $n=6$). (b) Effect of a combination of pyrilamine (2 mg/kg, i.v.) and ICI-192,605 (▲, A thromboxane receptor antagonist, 0.5 mg/kg, i.v., $n=6$) or pyrilamine and saline (●, 0.9% NaCl, $n=6$) on time course of lung resistance (R_L) induced by intratracheal instillation of 0.5% TMA-GPSA (50 μ l) in guinea-pigs 8 weeks after sensitization, compared with sensitized untreated animals (□, $n=7$).

induced bronchoconstriction was observed with a combination of a leukotriene antagonist or a lipoxygenase inhibitor with an antihistamine than with the antihistamine alone [7,14,16]. Thus, it is possible that guinea-pigs sensitized to TMA may have a slightly different mediator release to produce airflow obstruction compared with the OA-model [7,11,13–16].

The effects of a bronchoconstrictive stimuli depend partly on the baseline airway calibre. We found that the

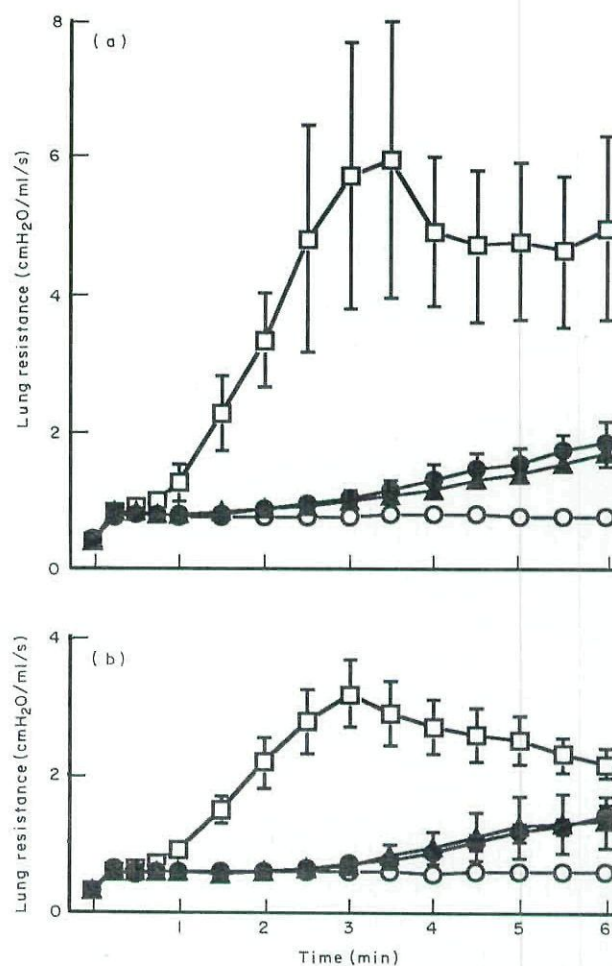


Fig. 2. (a) Effect of a combination of pyrilamine (2 mg/kg, i.v.) and ICI-198,615 (▲, A leukotriene receptor antagonist, 0.55 mg/kg, i.v., $n=6$) or pyrilamine and its vehicle (●, 2% PEG, $n=6$) on time course of lung resistance (R_L) induced by intratracheal instillation of 0.5% TMA-GPSA (50 μ l) in guinea-pigs 3 weeks after sensitization, compared with sensitized untreated animals (□, $n=6$). (b) Effect of a combination of pyrilamine (2 mg/kg, i.v.) and ICI-198,615 (▲, A leukotriene receptor antagonist, 0.55 mg/kg, i.v., $n=6$) or pyrilamine and the vehicle for ICI-198,615 (●, 2% PEG, $n=6$) on time course of lung resistance (R_L) induced by intratracheal instillation of 0.5% TMA-GPSA (50 μ l) in guinea-pigs 8 weeks after sensitization, compared with sensitized untreated animals (□, $n=7$).

older animals (8 weeks after sensitization) had a lower baseline R_L , compared with the younger group (3 weeks). Most likely, this difference in airway calibre depends on the growth of the animals, and therefore that the older animals have larger airways. The lower baseline R_L in the 8-week group may therefore have contributed to a weaker maximum R_L response in these animals.

TMA-GPSA induced airway plasma exudation was significantly attenuated by pyrilamine, confirming our

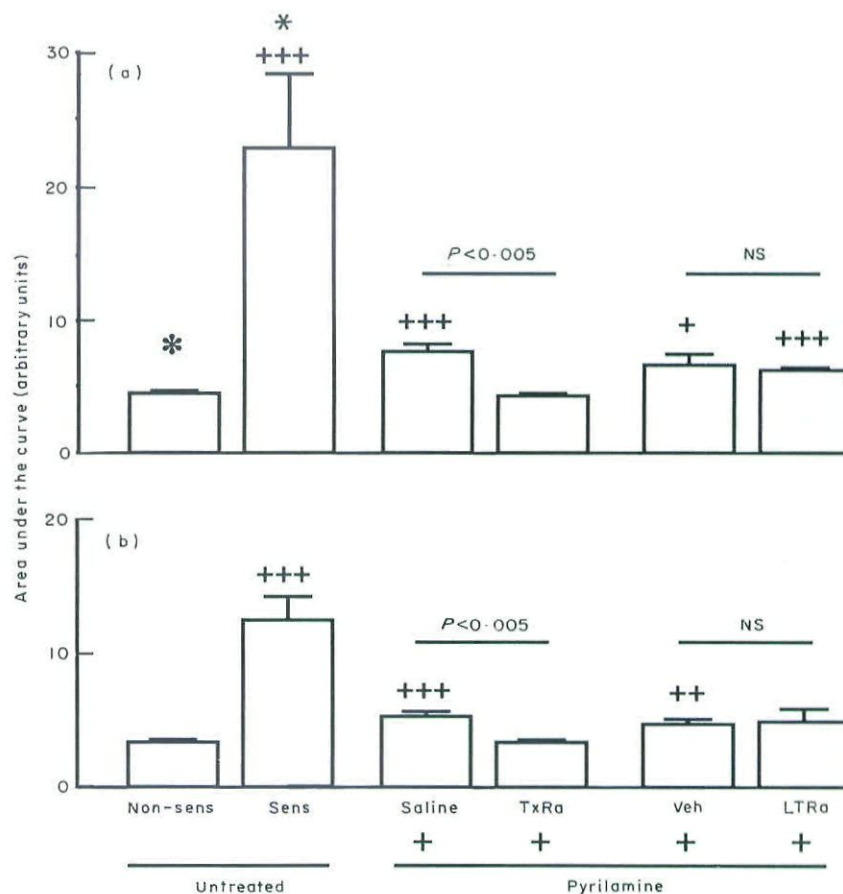


Fig. 3. Effect of various combination of antagonists on area under the curve (AUC) during observation periods (6 min) induced by instillation of TMA-GPSA in guinea-pigs 3 or 8 weeks after sensitization (a and b respectively). Data are shown as mean $\pm$ SEM. Non-sens. Non-sensitized animals challenged with TMA-GPSA 3 or 8 weeks later. Sens. Sensitized animals. T $\times$ Ra. ICI-192,605 (a thromboxane receptor antagonist). Veh. Vehicle for ICI-198,615. LTRa. ICI-198,615 (a leukotriene receptor antagonist). ICI-192,605, but not ICI-198,615, abolished AUC after the challenge. * $P < 0.05$ compared with the other age group. + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.005$ compared with non-sensitized untreated animals in the same week group.

previous findings [8,13]. In the present experiments, a combination of pyrilamine and a LT antagonist (ICI-198,615) significantly reduced the remaining extravasation of Evans Blue dye in intrapulmonary airways in animals challenged with TMA-GPSA 3 weeks, but not 8 weeks after sensitization. This would suggest that allergen-induced plasma exudation in part is mediated via LT production, at least early after sensitization. Several mediators have been suggested to be involved in allergen induced airway plasma exudation [8,13,15,16]. We have previously found that BW4AC, a 5-lipoxygenase inhibitor, slightly attenuates TMA-GPSA induced airway plasma exudation in sensitized guinea-pigs, but not significantly [13]. However, a LT antagonist (ICI-198,615) significantly reduced airway plasma exudation in another series of experiments [8]. The latter data are consistent with previous studies using animals sensitized to OA, showing that FPL55712, a LT receptor antagonist [15], and A-63162, a 5-lipoxygenase inhibitor [16], reduce allergen-induced airway plasma exudation. The remaining component of plasma exudation 8 weeks after sensitization, after pretreatment with the LT-receptor antagonist, may reflect release and *de novo* synthesis of other proinflammatory mediators [8,13,15,16]. In the

present study, a Tx antagonist (ICI-192,605) did not affect the remaining extravasation of Evans Blue dye in sensitized guinea-pig pretreated with pyrilamine, confirming our previous studies, indicating that TxA₂ is not involved in the TMA-induced airway plasma exudation [8].

Even though an almost complete inhibition of airway plasma exudation by a combination of pyrilamine and a LT antagonist was observed, no further attenuation of airflow obstruction compared with animals pretreated with pyrilamine alone was seen. This finding would suggest that contraction of the bronchial smooth muscle was important for the observed airflow obstruction. Also, in a previous study, we found significant attenuation of TMA-induced plasma exudation with a LT antagonist, without any effect on airflow obstruction [8], further arguing that plasma exudation only has minor effects on airflow obstruction in these models.

In asthmatic patients, LTs seems to be involved in the acute allergic responses, because of the release of LTE₄ in urine after allergen challenge [18]. Also, clear inhibitory effects are observed with LT receptor antagonist on allergen-induced early and late responses [19]. However, the role of TxA₂ in this disease seems to be minor. Tx

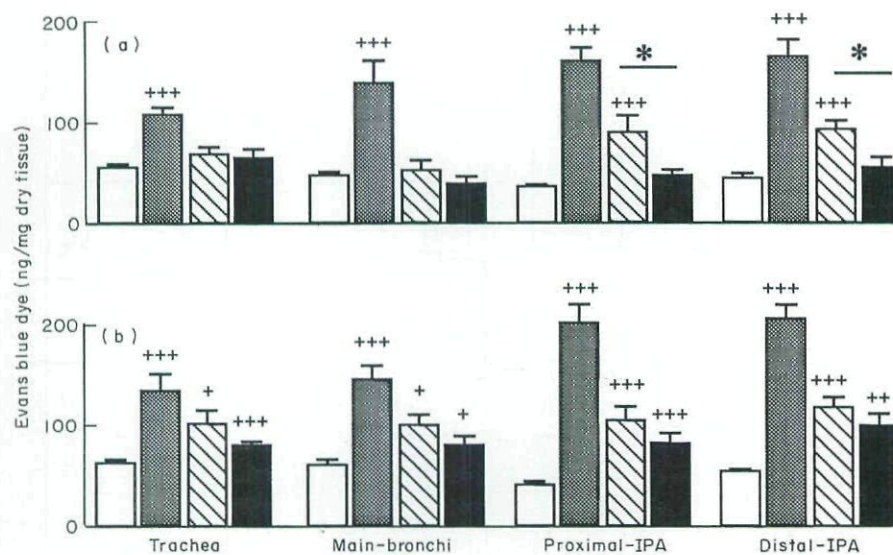


Fig. 4. Extravasation of Evans Blue dye (ng/mg dry tissue) induced by intratracheal instillation of TMA-GPSA in trachea, main-bronchi, and proximal and distal intrapulmonary airways in untreated guinea-pigs 3 and 8 weeks after intradermal injections with corn oil alone ($\square$) or free TMA ($\blacksquare$), and in animals pretreated with a combination of pyrilamine (2 mg/kg, i.v.) and ICI-198,615 (0.55 mg/kg, i.v.) ($\blacksquare$) or pyrilamine and the vehicle for ICI-198,615 ($\square$) 3 and 8 weeks after sensitization (a and b, respectively). Data are shown as mean $\pm$ SEM. IPA. Intrapulmonary. * $P < 0.05$ compared with sensitized animals pretreated with vehicle for ICI-198,615. + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.005$ compared with non-sensitized untreated animals in the corresponding week group.

Table 2. Effect of a combination of a thromboxane antagonist (ICI-192,605: 0.55 mg/kg, i.v.) and a histamine H_1 receptor antagonist (pyrilamine: 2 mg/kg, i.v.) on plasma exudation in the airways of guinea-pigs sensitized with TMA and challenged with trimellitic anhydride conjugated to guinea-pig serum albumin (TMA-GPSA) 3 or 8 weeks after sensitization.

	Evans Blue dye (ng/mg dry tissue)			
	Trachea	Main-bronchi	Proximal-IPA	Distal-IPA
<i>3 weeks after sensitization</i>				
Pyrilamine + saline	96 $\pm$ 13	80 $\pm$ 9	92 $\pm$ 13	92 $\pm$ 16
Pyrilamine + TxRa	87 $\pm$ 6	67 $\pm$ 10	57 $\pm$ 8	72 $\pm$ 9
<i>8 weeks after sensitization</i>				
Pyrilamine + saline	85 $\pm$ 5	94 $\pm$ 8	91 $\pm$ 10	115 $\pm$ 10
Pyrilamine + TxRa	96 $\pm$ 11	88 $\pm$ 7	75 $\pm$ 8	93 $\pm$ 7

Values are expressed as mean $\pm$ SEM. IPA, Intrapulmonary airways. TxRa, A thromboxane receptor antagonist (ICI-192,605).

receptor antagonists have a very small effect on the acute airflow obstruction induced by allergen in some experiments [20] but no effect in others [21].

This animal model of airway allergy to TMA mimics allergic occupational asthma, because of the similar capacity of allergen challenge to induce airflow obstruction [1]. Our present data suggest that the airflow obstruction induced by TMA-GPSA in actively sensitized guinea-pigs is mediated only via histamine and TxA_2 , whereas histamine and LTs are important in the induced

airway plasma exudation. However, at late time-points, other mediators may be involved in the allergen-induced airway plasma exudation. The role of eicosanoids in anhydride-induced airway plasma exudation in man is not known, and deserves further studies.

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