British Journal of Pharmacology (1995) 115, 1382-1386

Leukotriene receptors on human pulmonary vascular endothelium

J.L. Ortiz, †I. Gorenne, J. Cortijo, A. Seller, †C. Labat, B. Sarria, *T.S. Abram, *P.J. Gardiner, E. Morcillo & †[1]C. Brink

Departament de Farmacologia, Universitat de Valencia, Valencia, Spain; *Bayer UK Ltd, Pharmaceutical Business Group, Research Department, Stoke Poges, U.K. and †Centre Chirurgical Marie Lannelongue, CNRS URA 1159, Le Plessis-Robinson, France

1 Cysteinyl-leukotrienes cause contractions and/or relaxations of human isolated pulmonary vascular preparations. Although, the localization and nature of the receptors through which these effects are mediated have not been fully characterized, some effects are indirect and not mediated via the well-described LT_1 receptor.

2 In human pulmonary veins (HPV) with an intact endothelium, leukotriene D_4 (LTD_4) induced contraction above basal tone. This response was observed at lower concentrations of LTD_4 in the presence of nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine (L-NOARG). Contractions (in the absence and presence of L-NOARG) were partially blocked by the LT_1 antagonists (MK 571 and ICI 198615).

3 LTD_4 relaxed HPV previously contracted with noradrenaline. This relaxation was potentiated by LT_1 antagonists, but was abolished by removal of the endothelium. LTD_4 also relaxed human pulmonary arteries (HPA) precontracted with noradrenaline but this effect was not modified by LT_1 antagonists.

4 The results suggest that contraction of endothelium-intact HPV by LTD_4 is partially mediated via LT_1 receptors. Further, in endothelium-intact HPV, this contraction was opposed by a relaxation induced by LTD_4, dependent on the release of nitric oxide, which was mediated, at least in part, via a non-LT_1 receptor. In addition, LTD_4 relaxation on contracted HPA was not mediated by LT_1 receptors.

5 The mechanical effects of LTD_4 on human pulmonary vasculature are complex and involve both direct and indirect mechanisms mediated via at least two types of cysteinyl-leukotriene receptors.

Keywords: Leukotriene receptors; nitric oxide; endothelium; human pulmonary vessels

Introduction

A considerable amount of evidence has been published demonstrating the contractile effects of leukotrienes (LT) in a variety of smooth muscle preparations from several animal species including man (Dahlén *et al.*, 1980; Hanna *et al.*, 1981; Buckner *et al.*, 1986; Bourdillat *et al.*, 1987). However, LT are also known to produce endothelium-dependent relaxations in vessels from different species (Burke *et al.*, 1982; Secrest *et al.*, 1985; Sakuma & Levi, 1988). Endothelium-dependent relaxations are mediated via factors such as prostacyclin (Moncada *et al.*, 1976) or nitric oxide (NO) (Furchgott & Zawadski, 1980; Ignarro *et al.*, 1987; Palmer *et al.*, 1987).

In an early report, Secrest and coworkers (1985) suggested that leukotriene D_4 (LTD_4) induced relaxations in canine renal and superior mesenteric arteries were produced by stimulation of an LT receptor, since the LT antagonist, FPL 55712 attenuated the LT relaxant responses. Recently, Pawloski & Chapnick (1993) showed that stimulation of these LT receptors induced relaxations which were associated with activation of the nitric oxide pathway. These observations supported previous results (Secrest *et al.*, 1988) which demonstrated that LTD_4 increased guanosine 3':5'-cyclic monophosphate (cyclic GMP) accumulation in canine vessels. Such data suggested that the LT receptor on the endothelium was intimately linked to the nitric oxide pathway. However, results obtained in the guinea-pig respiratory tract (Fleisch *et al.*, 1982; Krell *et al.*, 1983) and recent data obtained from the human lung suggested that there may be several LT receptors, namely LT_1 and LT_2 in this latter tissue (Labat *et al.*, 1992). Since FPL 55712 is a nonselective LT antagonist (Chasin & Scott, 1978; Welton *et al.*, 1981), the specific LT receptors involved in vascular relaxations are at present unknown. The aim of this investigation was to characterize the LT receptors located on the endothelium in human isolated pulmonary vascular preparations.

[1]Author for correspondence at: Centre Chirurgical Marie Lannelongue, CNRS URA 1159, 133 ave de la Résistance, 92350 Le Plessis Robinson, France.

Methods

Human pulmonary arteries and veins were dissected from lung samples obtained from patients who had undergone surgery for lung carcinoma. Arteries and veins were separated from adjacent parenchymal tissues and the preparations were cut as rings set up under a load of 2 g in 10 ml organ baths. Tissues were used 1–3 h post surgery, since preparations stored overnight failed to relax when stimulated with 0.1 μM histamine (endothelium-dependent relaxation). The composition of the Tyrode solution was (mM concentrations): NaCl 139.2, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 0.49, $NaHCO_3$ 11.9, NaH_2PO_4 0.4, glucose 5.5, pH 7.4. Ring preparations were allowed to equilibrate for 90 min at 37°C and were continuously gassed with 5% CO_2 in O_2. Contractions and relaxations were monitored with isometric force transducers (Narco F-60) and Linseis recorders.

Relaxation protocols

Following the equilibration period, preparations were contracted with noradrenaline (1 μM) and relaxed with histamine (1 μM) to confirm endothelium function. The tissues were then washed and when resting tone was re-established the preparations were incubated for 30 min with Tyrode solution with or without the following drugs: ICI 198615 (1 μM; 30 min), MK 571 (1 μM; 30 min); L-NOARG (100 μM; 15 min). The LT

antagonists were also used in combination with NO synthase inhibitor L-NOARG at the concentrations indicated. The tissues were subsequently contracted with noradrenaline and when the response reached a plateau increasing concentrations of LTD_4 were added to the tissue baths. Similar experiments were performed in tissues where the endothelium had been removed by gently rubbing the luminal surface with a moistened cotton swab. The LTD_4 relaxation was not always observed (approximately 50% of samples), even though tissues always relaxed with histamine (0.1 μM).

Contraction protocols

After the 90 min equilibration period the ring preparations were contracted with noradrenaline (10 μM) and, when the response reached a plateau, histamine (1 μM) was added to the tissue baths. The tissues were washed until resting tone was re-established before being incubated (30 min) with ICI 198615 (1 μM), MK 571 (1 μM) and/or L-NOARG (100 μM). Following drug treatment, a concentration-effect curve was produced by adding increasing concentrations of LTD_4 in a cumulative fashion. Several experiments were also performed in tissues in which the endothelium had been removed by rubbing the luminal surface.

Calculations

Changes in force were expressed in g and results presented as percentage of the maximal response induced by noradrenaline (10 μM) and are means ± s.e.mean. The EC_{50} values were obtained from cumulative concentration-effect curves by linear regression analysis of data points from individual concentration-effect curves. The EC_{50} values were transformed into pD_2 values (–log EC_{50}). Statistical analysis was performed by ANOVA followed by Student's *t* test for paired or unpaired variables as appropriate. The correlation analysis was performed using the Pearson test.

Drugs

The drugs used were: histamine dihydrochloride, noradrenaline and N^{ω}-nitro-L-arginine (L-NOARG) (Sigma Chemical Co. St. Louis MO. U.S.A.). All LT and antagonists ICI 198615 ((1-[2-methoxy-4-{([phenylsulphonylamino]carbonyl)phenyl}methyl]-1*H*-indazol-6-yl)carbamic acid cyclopentyl ester)) and MK 571 ([3-{-2(7-chloro-2-quinolinyl)ethenyl}phenyl][{3-(dimethylamino-3-oxopropyl)thio}methyl]thio propanoic acid) were synthesized at Bayer plc (Stokes Poges, Great Britain and Wuppertal, Germany).

Results

Relaxation

LTD_4 induced a relaxation in endothelium-intact human pulmonary arteries and veins which had been contracted with noradrenaline (1 μM; Figure 1). In venous ring preparations which had been treated with either ICI 198615 (1 μM) or MK 571 (1 μM) the LTD_4 relaxant response was markedly enhanced. In contrast, no significant alteration in relaxation was observed in intact pulmonary arteries. Furthermore, LTD_4-induced relaxation was not observed in either pulmonary arteries or veins where the endothelium had been removed (rubbed tissues; data not shown).

Contraction

In pulmonary veins there was a correlation between the endothelium-dependent relaxation (measured by histamine challenge) and the contractions induced by LTD_4 (Figure 2: $r^2 = 0.68$; $P < 0.006$). In intact preparations treated with L-NOARG, an inhibitor of endogenous NO release, this correlation was not observed ($r^2 = 0.34$; $P > 0.13$).

The data presented in Figure 3 show that the LTD_4-induced contractions were not altered after removal of endothelium by rubbing. In contrast, vessels treated with L-NOARG exhibited an increased sensitivity to LTD_4 (Table 1). However, the maximal contractions were not significantly different (intact preparations: 2.64 ± 0.67 g; rubbed preparations: 2.43 ± 0.54 g and intact preparations treated with L-NOARG 100 μM: 3.53 ± 0.63 g).

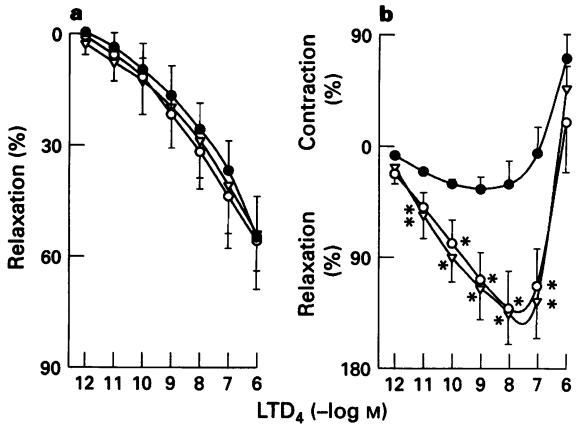

Figure 1 Leukotriene D_4 (LTD_4)-induced relaxations of human pulmonary vessels. Preparations were contracted with noradrenaline (1 μM) and relaxed with histamine (1 μM). Following a washing period the preparations were incubated (30 min) either with vehicle (control, ●) or different LT_1 antagonists (ICI 198615, 1 μM, ▽; MK 571, 1 μM, ○). Preparations were contracted with noradrenaline and relaxed with LTD_4. The results are presented as % of the noradrenaline (1 μM)-induced contraction (arteries, 1.08 ± 0.11 g and veins, 1.49 ± 0.52 g). (a) Human pulmonary arteries; (b) human pulmonary veins. Values are mean ± s.e.mean from 6 paired lung samples. Statistical analysis was performed using ANOVA followed by Student's *t* test for paired samples. *Indicates values significantly different from appropriate control results with Student's *t* test ($P < 0.05$).

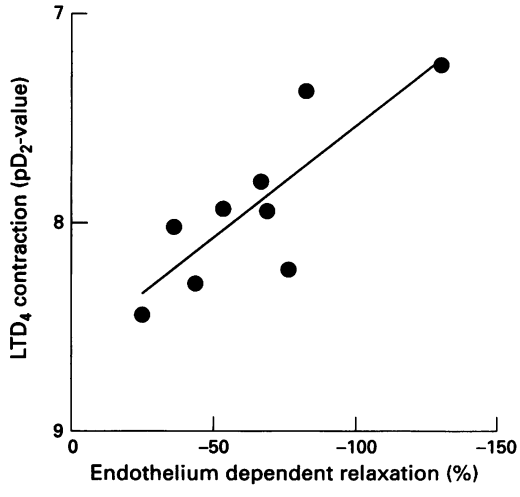

Figure 2 Correlation between leukotriene D_4 (LTD_4)-induced contractions of human pulmonary veins and the endothelium-dependent relaxation. The preparations were incubated (30 min) with vehicle and the contractions induced by LTD_4 were obtained. The pD_2 values for LTD_4 were obtained from the LTD_4 concentration-effect curves (EC_{50}) and transformed to pD_2 values (–log M). The histamine (1 μM)-induced relaxation (index of a functional endothelium) are presented as % of the noradrenaline (1 μM)-induced contraction. Values are from 9 lung samples. Statistical analysis was performed using the Pearson Correlation test ($r^2 = 0.68$; $P < 0.006$).

In the presence of ICI 198615 (1 μM) or MK 571 (1 μM) the LTD_4-induced contractions were partially blocked in intact pulmonary veins (Figure 4 and Table 1). However, the shifts observed with these antagonists were not concentration-related. Similar data were obtained in tissues treated with these antagonists in the presence of L-NOARG (Figure 5 and Table 1). No shift in the LTD_4 curves was observed in rubbed tissues treated with either ICI 198615 or MK 571 (Figure 6).

Discussion

The results obtained in this study demonstrate that LTD_4 induced both contraction and relaxation of human pulmonary vascular tissues, findings which are in agreement with previously published results (Schellenberg & Foster, 1984; Sakuma *et al.*, 1987; Bourdillat *et al.*, 1987; Allen *et al.*, 1992; Pawloski & Chapnick, 1993). The relaxant effects may depend on the type of vessel and/or the species from which the preparations are derived, since there are some reports which have shown no LTD_4-induced relaxation of isolated vascular preparations from the rabbit or guinea-pig (Berkowitz *et al.*, 1984). A few studies (Secrest *et al.*, 1985; Labat *et al.*, 1992) have explored the LT-receptors present in isolated vessels. Secrest and coworkers (1985) using canine vascular preparations demonstrated that stimulation of the LT receptor which lead to vascular relaxation was inhibited by FPL 55712. However, Chasin & Scott (1978), reported that FPL 55712 inhibited phosphodiesterase in cells and Welton and coworkers (1981) showed that release of mediators such as histamine and thromboxane was blocked by FPL 55712, suggesting that this compound is not only a LT-receptor antagonist.

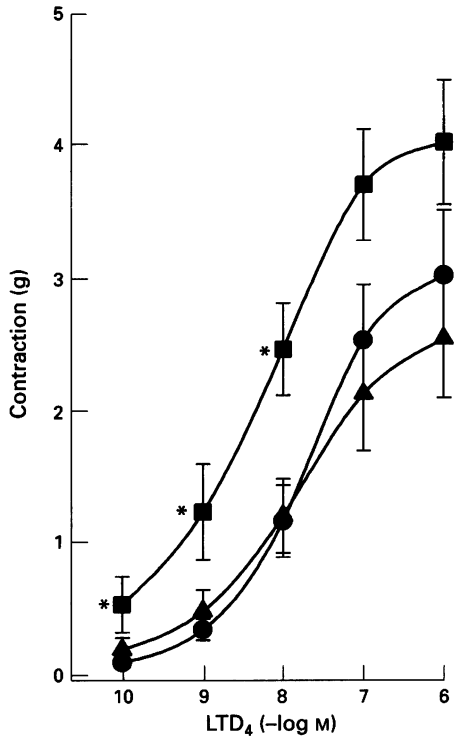

Figure 3 Leukotriene D_4 (LTD_4)-induced contractions of human pulmonary veins. LTD_4 concentration-effect curves were produced in intact tissues (●), intact tissues treated with N^{ω}-nitro-L-arginine (L-NOARG, 100 μM, ■) and tissues after removal of endothelium (▲). The results are presented as force (g) of the LTD_4-induced contraction. Values are mean ± s.e.mean from 5–6 lung samples. Statistical analysis was performed using the ANOVA followed by the Student's *t* test for paired samples. *Indicates values significantly different from appropriate control results using Student's *t* test ($P < 0.05$).

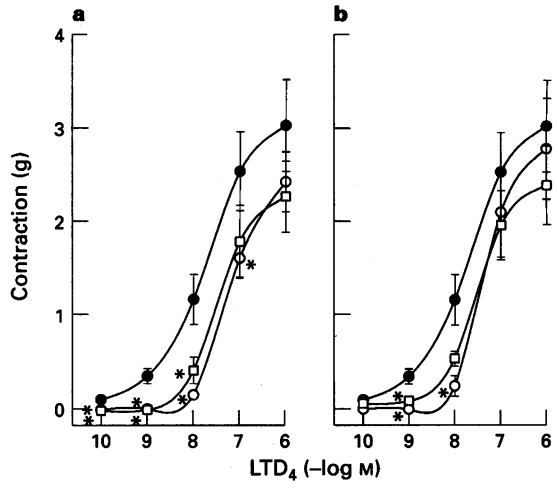

Figure 4 Effects of LT_1 antagonists on leukotriene D_4 (LTD_4)-induced contractions in intact pulmonary veins. The preparations were incubated (30 min) either with vehicle (control; ●) or different LT_1 antagonists and LTD_4 curves were produced. (a) MK 571, 0.1 μM (□) and 1 μM (○). (b) ICI 198615, 0.1 μM (□) and 1 μM (○). The results are presented as force (g) of the LTD_4-induced contraction. Values are mean ± s.e.mean from 6–7 lung samples. Statistical analysis was performed using the ANOVA followed by the Student's *t* test for paired samples. *Indicates values significantly different from appropriate control results using Student's *t* test ($P < 0.05$).

Table 1 pD_2 values obtained from leukotriene D_4 (LTD_4) curves in human pulmonary veins in absence or presence of LT_1 antagonists (ICI 198615 and MK 571)

	LTD_4 contractions (pD_2 values)					
	n	*Control*	*n*	*L-NOARG* (100 μM)	*n*	*Rubbed*
Non treated	9	7.92 ± 0.13	8	8.60 ± 0.24[a]	8	7.96 ± 0.16
MK 571						
0.1 μM	6	7.41 ± 0.08*	6	7.54 ± 0.07*		
1 μM	6	7.27 ± 0.05*	8	7.61 ± 0.10*	6	7.78 ± 0.09
ICI 198615						
0.1 μM	7	7.61 ± 0.07	6	7.77 ± 0.15*		
1 μM	6	7.30 ± 0.07*	6	7.56 ± 0.09*	5	7.73 ± 0.14

Control (intact tissues), L-NOARG (treated tissues) and Rubbed (without endothelium). Results are mean ± s.e.mean of *n* lung samples. *Values significantly different from appropriate non-treated tissues; [a] values significantly different from non-treated control group.

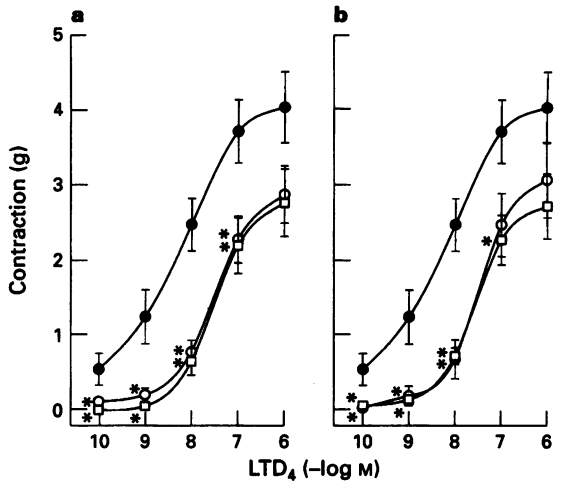

Figure 5 Effects of LT_1 antagonists on leukotriene D_4 (LTD_4)-induced contractions in intact pulmonary veins in presence of N^{ω}nitro-L-arginine (L-NOARG, 100 μM). The preparations were incubated (30 min) either with L-NOARG (100 μM; ●) or different LT_1 antagonists in the presence of L-NOARG (100 μM) and LTD_4 curves were produced. (a) MK 571, 0.1 μM (□) and 1 μM (○). (b) ICI 198615, 0.1 μM (□) and 1 μM (○). The results are presented as force (g) of the LTD_4-induced contraction. Values are mean ± s.e.mean from 6–7 lung samples. Statistical analysis was performed by ANOVA followed by Student's *t* test for paired samples. *Indicates values significantly different from appropriate control results using Student's *t* test ($P < 0.05$).

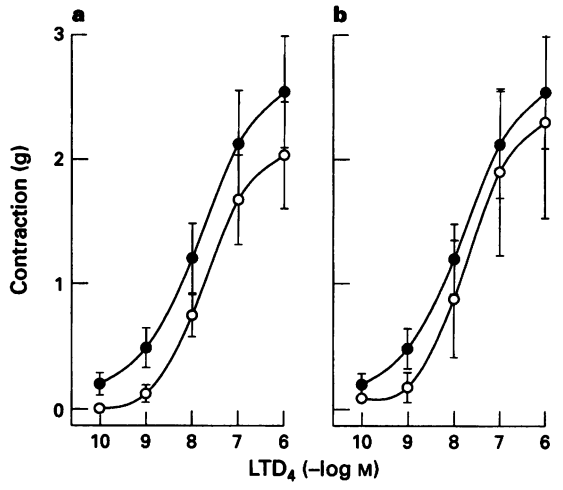

Figure 6 Effects of LT_1 antagonists on leukotriene D_4 (LTD_4)-induced contractions in rubbed human pulmonary veins. The preparations were incubated (30 min) either with vehicle (control, ●) or different LT_1 antagonists and LTD_4 curves were produced. (a) MK 571, 1 μM (○); (b) ICI 198615, 1 μM (○). The results are presented as force (g) of the LTD_4-induced contraction. Values are mean ± s.e.mean from 6–7 lung samples. Statistical analysis was performed by ANOVA followed by the Student's *t* test for paired samples.

The data (present paper) demonstrate that LTD_4-induced relaxation of human isolated pulmonary vessels is endothelium-dependent via relaxing factors since removal of the endothelium abolished this response. In addition, in human pulmonary veins there are two receptors present on the endothelium. One is associated with LTD_4-induced relaxation and resistant to LT_1 antagonists; a second receptor is associated with LTD_4 contractions and blocked by LT_1 antagonists. The evidence derived from human isolated pulmonary vessels which support these observations are as follows. LTD_4-induced relaxations of human isolated pulmonary veins were potentiated by the LT_1 antagonists, ICI 198615 or MK 571. The more pronounced relaxation which was unmasked in the presence of an LT_1 antagonist suggests that an LT_1 receptor is involved in the contraction. Furthermore, LTD_4-induced relaxations of human isolated pulmonary arteries were not blocked by ICI 198615 or MK 571 (Figure 1), suggesting that the receptor which mediates relaxation is not LT_1.

Since the endothelium releases relaxing factors (Furchgott & Zawadski, 1980; Ignarro *et al.*, 1987; Moncada *et al.*, 1987) as well as substances which induce contraction (Vanhoutte *et al.*, 1991), the paradoxical effects of the leukotrienes in different vessels (Nishiye *et al.*, 1988; Sakuma & Levi, 1988; Fedyna *et al.*, 1990; Rosenblum *et al.*, 1990; McLeod & Piper, 1992) may be due to those factors which are released during stimulation of specific leukotriene receptors on the endothelium. Treatment of intact venous preparations with the NO synthase inhibitor, L-NOARG, caused a significant leftward shift of the LTD_4 curves, suggesting that the relaxing factor, NO, may antagonize LTD_4 contractions. However, in the absence of the endothelium, the LTD_4-induced contractions of human pulmonary venous preparations were identical to those of control tissues but significantly different from those obtained in L-NOARG-treated vessels. One interpretation of these results is that the contraction induced by LTD_4 is not only due to the stimulation of the vascular smooth muscle but also to the endothelium. In intact pulmonary venous preparations the LT_1 antagonists (ICI 198615 and MK 571) caused a partial block of the LTD_4 contractions either in the presence or absence of L-NOARG. However, this inhibition was not concentration-dependent. These compounds are potent LT_1 antagonists but the receptors present on the human pulmonary venous vascular smooth muscle are LT_2 receptors (Labat *et al.*, 1992). Therefore, the slight displacement observed is due to inhibition of a contractile component mediated by the LT_1 receptor present on the endothelium. In addition, after removal of the endothelium there was no shift in the LTD_4 contraction curves by either of these LT_1 antagonists. Therefore, only a partial inhibition by LT_1 antagonists can be observed since the dominant effect of LTD_4 in human pulmonary veins is contraction via LT_2 receptors on the vascular muscle. Results obtained in rubbed preparations (Figure 5) confirm previous findings that LT_1 antagonists have no effect on LTD_4-induced contractions of human isolated pulmonary veins (Labat *et al.*, 1992). These latter results were obtained in intact tissues stored for 12 h where endothelium-dependent relaxations were absent.

These data provide evidence that the LTD_4 relaxant effect was endothelium-dependent via release of NO, and this relaxant activity via an LT receptor may offset the LTD_4 contractions. In addition, these data suggest that there is an LT_1 receptor present on the endothelium which is associated with LTD_4 contractions. At present there are no data to confirm whether the receptor (LT_2) reported on human isolated pulmonary veins (Labat *et al.*, 1992) is distinct from or similar to the LTD_4 receptor on the endothelium associated with relaxation.

Part of this work has been supported by grants FAR 90-680 and FAR 91-0875 of CICYT (Ministerio de Industria y Energia) Spain.

References

ALLEN, S.P., CHESTER, A.H., PIPER, P.J., SAMPSON, A.P., AKL, E.S.K. & YACOUB, M.H. (1992). Effects of leukotrienes C_4 and D_4 on human isolated saphenous veins. *Br. J. Clin. Pharmacol.*, **34**, 409–414.

BERKOWITZ, B.A., ZABKO-POTAPOVICH, B., VOLOCIK, R. & GLEASON, J.G. (1984). Effects of the leukotrienes on the vasculature and blood pressure of different species. *J. Pharmacol. Exp. Ther.*, **229**, 105–112.

BOURDILLAT, B., HAYE-LEGRAND, I., LABAT, C., RAFFESTIN, B., NOREL, X., BENVENISTE, J. & BRINK, C. (1987). Effects of various pharmacological agents on isolated human bronchial and pulmonary arterial and venous muscle preparations contracted with leukotriene D_4. *Fundam. Clin. Pharmacol.*, **1**, 433–444.

BUCKNER, C.K., KRELL, R.B., LARAVUSO, R.B., COURSIN, D.B., BERNSTEIN, P.R. & WILL, J.A. (1986). 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.*, **237**, 558–562.

BURKE, J.A., LEVI, R., GUO, Z.G. & COREY, E.J. (1982). Leukotrienes C_4, D_4 and E_4: Effects on human and guinea-pig cardiac preparations in vitro. *J. Pharmacol. Exp. Ther.*, **221**, 235–241.

CHASIN, M. & SCOTT, C. (1978). Inhibition of cyclic nucleotide phosphodiesterase by FPL 55712 an SRS-A antagonist. *Biochem. Pharmacol.*, **27**, 2065–2067.

DAHLEN, S.E., HEDQVIST, P., HAMMARSTRÖM, S. & SAMUELSSON, B. (1980). Leukotrienes are potent constrictors of human bronchi. *Nature*, **288**, 484–486.

FEDYNA, J.S., SNYDER, D.W., AHARONY, D., REDKAR-BROWN, D. & KRELL, R.D. (1990). Pharmacologic characterization of the contractile activity of peptide leukotrienes in guinea-pig pulmonary artery. *Prostaglandins*, **39**, 541–558.

FLEISCH, J.H., RINKEMA, L.E. & BAKER, S.R. (1982). Evidence for multiple leukotriene D_4 receptors in smooth muscle. *Life Sci.*, **31**, 577–581.

FURCHGOTT, R.F. & ZAWADZKI, J.V. (1980). The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature*, **288**, 373–376.

HANNA, C.J., BACH, M.K., PARE, P.D. & SCHELLENBERG, R.R. (1981). Slow reacting substances (leukotrienes) contract human airway and pulmonary vascular smooth muscle in vitro. *Nature*, **290**, 343–344.

IGNARRO, J., BYRNS, R.E. & WOODS, K.S. (1987). Endothelium-dependent modulation of cGMP levels and intrinsic smooth muscle tone in isolated bovine intrapulmonary artery and vein. *Circ. Res.*, **60**, 82–92.

KRELL, R.D., TSAI, B.S., BERDOULAY, A., BARONE, M. & GILES, R.E. (1983). Heterogeneity of leukotriene receptors in guinea-pig trachea. *Prostaglandins*, **25**, 171–178.

LABAT, C., ORTIZ, J.L., NOREL, X., GORENNE, I., VERLEY, J., ABRAMS, T.S., CUTHBERT, N.J., TUDHOPE, S.R., NORMAN, P., GARDINER, P.J. & BRINK, C. (1992). A second cysteinyl leukotriene receptor in human lung. *J. Pharmacol. Exp. Ther.*, **263**, 800–805.

McLEOD, J.D. & PIPER, P.J. (1992). Effect of removing the endothelium on the vascular responses induced by leukotrienes C_4 and D_4 in guinea-pig isolated heart. *Eur. J. Pharmacol.*, **212**, 67–72.

MONCADA, S., GRYGLEWSKI, R., BUNTING, S. & VANE, J.R. (1976). An enzyme isolated from arteries transform prostaglandin endoperoxydase to an unstable substance that inhibits platelet aggregation. *Nature*, **263**, 663–665.

NISHIYE, E., ITOH, T. & KURIYAMA, H. (1988). Some effects of leukotriene D_4 on the mechanical properties of the guinea-pig basilar artery. *Br. J. Pharmacol.*, **93**, 591–600.

PALMER, R.M.J., FERRIGE, A.G. & MONCADA, S. (1987). Nitric oxide release accounts for the biological activity of endothelium derived relaxing factors. *Nature*, **327**, 524–526.

PAWLOSKI, J.R. & CHAPNICK, B.M. (1993). Leukotriene C_4 and D_4 are potent endothelium dependent relaxing agents in canine splanchnic venous capacitance vessels. *Circ. Res.*, **73**, 395–404.

ROSENBLUM, W.I., NELSON, G.H. & NISHIMURA, H. (1990). Leukotriene constriction of mouse pial arterioles in vivo is endothelium-dependent and receptor mediated. *Stroke*, **21**, 1618–1620.

SAKUMA, I., GROSS, S.S. & LEVI, R. (1987). Peptidoleukotrienes induced an endothelium-dependent relaxation of guinea pig main pulmonary artery and thoracic aorta. *Prostaglandins*, **34**, 685–696.

SAKUMA, I. & LEVI, R. (1988). Vasomotor effects of leukotrienes C_4 and D_4 on cavian pulmonary artery and aorta. *Ann. N.Y. Acad. Sci.*, **524**, 91–102.

SCHELLENBERG, R.R. & FOSTER, A. (1985). Differential activity of leukotrienes upon human pulmonary vein and artery. *Prostaglandins*, **27**, 475–482.

SECREST, R.J., OHLSTEIN, E.H. & CHAPNICK, B.M. (1988). Relationship between LTD_4-induced endothelium-dependent vasomotor relaxation and cGMP. *J. Pharmacol. Exp. Ther.*, **245**, 47–52.

SECREST, R.J., OLSEN, E.J. & CHAPNICK, B.M. (1985). Leukotriene D_4 relaxes canine renal and superior mesenteric arteries. *Circ. Res.*, **57**, 323–329.

VANHOUTTE, P.M., LUSCHER, T.F. & GRASER, T. (1991). Endothelium dependent contractions. *Blood Vessels*, **28**, 74–83.

WELTON, A.F., HOPE, W.C., TOBIAS, L.D. & HAMILTON, J.G. (1981). Inhibition of antigen-induced histamine release and thromboxane synthase by FPL 55712, a specific SRS-A antagonist? *Biochem. Pharmacol.*, **30**, 1378–1382.

(Received October 17, 1994
Revised March 30, 1995
Accepted May 3, 1995)