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BAY u3405, a potent and selective thromboxane A_2 receptor antagonist on airway smooth muscle *in vitro*

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1 BAY u3405 (3(**R**)-[[(4-fluorophenyl) sulphonyl]amino]-1,2,3,4-tetrahydro-9H-carbazole-9-propanoic acid) has been evaluated on airway smooth muscle, from a number of species including man, for its thromboxane A_2 (TXA_2) antagonist activity.

2 BAY u3405 was a potent, and competitive, antagonist of the TXA_2-mimetic U46619-induced contractions of human, guinea-pig, rat and ferret airway smooth muscle with pA_2 values between 8.0 and 8.9 and with no inherent contractile activity (10^{-9}–10^{-4} M).

3 The TXA_2 antagonist activity of BAY u3405 was stereoselective. Its (S)-enantiomer, BAY u3406, was approximately 50 fold less effective against U46619 on guinea-pig and human airway smooth muscle.

4 BAY u3405 also competitively antagonized contractions of guinea-pig airway smooth muscle induced by prostaglandin D_2 (PGD_2) or its metabolite 9α, 11β-PGF_2. On human and ferret airway smooth muscle it abolished contractions induced by PGD_2, $PGF_{2\alpha}$ and 16, 16-dimethyl-PGE_2.

5 A high concentration (10^{-6} M) of BAY u3405 had no effect on the contraction, or relaxation, of airway smooth muscle induced by a range of other agonists, nor did BAY u3405 have any effect on other prostanoid receptor types (DP, EP_1, EP_2, FP or IP).

6 BAY u3405, in contrast to some other TXA_2 antagonists, is a potent and selective antagonist on a wide range of airways including human. This high affinity, and the oral activity of the compound described elsewhere, suggest it may be an appropriate tool to investigate the role of prostanoids in airway diseases such as asthma.

Keywords: BAY u3405; thromboxane antagonists; PGD_2; $PGF_{2\alpha}$; TXA_2 receptor; 9α, 11β-PGF_2; human bronchial muscle; human lung strip

Introduction

It has been postulated that thromboxane A_2 (TXA_2) may be significantly involved in various diseases including asthma (Ogletree, 1987). In the past, non-steroidal anti-inflammatory drugs (NSAID) have been used as tools to investigate such a possibility but with limited success (Fairfax *et al.*, 1983, Shephard *et al.*, 1985). However such drugs inhibit the production of all cyclo-oxygenase products and consequently they have the potential to inhibit the beneficial bronchodilator effect of prostaglandin E_2 (PGE_2). It seemed possible (although never substantiated in asthmatics) that NSAID also induce shunting of arachidonic acid to the lipoxygenase pathway culminating in the synthesis of leukotrienes which are also thought to be pathological mediators of asthma. (Walker, 1980; Kuehl *et al.*, 1984). Consequently NSAID seem inappropriate tools to investigate the role of TXA_2 in asthma.

Considerable effort was assigned to the identification of more specific pharmacological tools to inhibit/antagonize TXA_2. A range of thromboxane synthase inhibitors were shown to inhibit selectively the synthesis of TXA_2 and as such represented valuable new tools in this area (Cross & Dickinson, 1987). Although such compounds inhibited TXA_2 synthesis, activation of TXA_2 receptors was still possible due to the presence of higher levels of PGH_2 and PGD_2; consequently such tools also have limited possibilities.

The identification of TXA_2 antagonists seemed a more useful target in this area. A critical prerequisite in the identification of such compounds was a general understanding of the TXA_2 receptor type(s) implicated in asthma. Evidence from some studies using platelets and smooth muscle suggested that TXA_2 receptor subtypes existed (Lefer *et al.*, 1980; Mais *et al.*, 1988). We proposed that human airway smooth muscle had more than one subtype present (McKenniff *et al.*, 1988). It seemed likely that TXA_2 antagonists which would be useful for investigation in asthma, should antagonize all TXA_2 receptor subtypes, or at least all of those present in human airways.

In this series of studies we describe for the first time extensive studies with the TXA_2 antagonist, BAY u3405. This novel indole sulphonamide (Figure 1) which is a TXA_2 antagonist on platelets and vascular smooth muscle (Rosentreter *et al.*, 1989) is also a potent and selective TXA_2 antagonist in airway smooth muscle from a wide range of species including man. Due to the poor stability of TXA_2, the TXA_2-mimetic, U46619 (Coleman *et al.*, 1981) was used in these studies.

Methods

Isolated respiratory tissues

Airway smooth muscle preparations were prepared as previously described (McKenniff *et al.*, 1988; 1989) save that

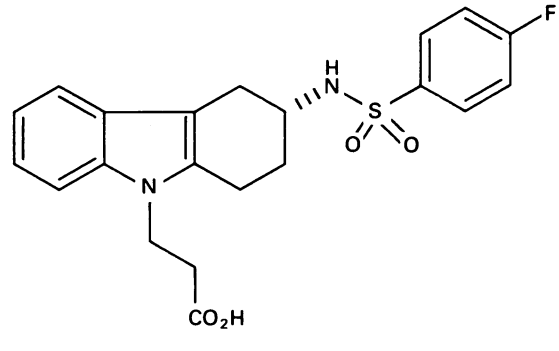

Figure 1 The chemical structure of BAY u3405: 3 (**R**)-[[(4-fluorophenyl) sulphonyl] amino]-1,2,3,4-tetrahydro-9H-carbazole-9-propanoic acid.

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indomethacin (3×10^{-6} M) was used rather than flurbiprofen. In brief, lung strips were taken from the periphery of the lung and set up under a resting tension of 0.5 g. Tracheae were set up as single rings with a resting tension of 1.0 g.

Rat lung strips from male Wistar rats (250–300 g) were prepared as described for the guinea-pig and human lung strip and set up at a resting tension of 1.0 g. In studies with leukotriene C_4 (LTC_4) and LTD_4 the bathing solution also contained 4.5×10^{-2} M L-serine borate and 10^{-2}M L-cysteine to inhibit the metabolism of these leukotrienes. All tension changes were measured isometrically.

Experimental design

Preparations were left to equilibrate for 1 h with washes every 15 min. Tissue viability was determined by addition of KCl (5×10^{-2} M). After washing and 30 min re-equilibration, antagonists were added and left in contact with the preparation for 60 min before the cumulative addition of increasing concentrations of the agonist. Only one agonist concentration-response curve was obtained from each preparation and KCl (5×10^{-2} M) was then added to obtain a maximal contractile response for normalisation of responses. Consequently paired preparations (i.e. one preparation treated with a vehicle control and the other with the test antagonist) were used to determine the degree of antagonism relative to the control agonist response.

Selectivity at other receptor types

Non-prostanoids The effect of BAY u3405 (10^{-6} or 10^{-5} M) was evaluated by the same procedure as described above against the following contractile agonists on the airway smooth muscle preparation indicated. Cumulative concentration-response curves to the test agonist were constructed in each case; guinea-pig trachea: carbachol, histamine, 5-hydroxytryptamine, LTC_4 and LTD_4; human lung strip: LTD_4; rat lung strip: carbachol. The effect of BAY u3405 on the isoprenaline-induced relaxation of guinea-pig tracheal rings contracted with histamine was also determined.

Prostanoids The effect of BAY u3405 (10^{-6} M) was also examined against a range of prostanoids on the following tissues. The setting up of tissues and the procedures used were the same as those described by the following groups:— PGI_2, PGD_2 and BW 245C-induced relaxations of rabbit jugular veins (Giles *et al.*, 1989), 16,16-dimethyl-PGE_2 and $PGF_{2\alpha}$-induced contractions and butaprost-induced relaxation of guinea-pig trachea (McKenniff *et al.*, 1988) and finally $PGF_{2\alpha}$- and fluprostenol-induced contractions of rat colon (Eglen & Whiting, 1988).

Spasmogenic activity on airway smooth muscle

Human and guinea-pig airway smooth muscle was prepared as described above, save that studies were also carried out with indomethacin omitted from the bathing solution. After the response to KCl had been determined and resting tension re-established a single concentration of BAY u3405 between 10^{-9} and 10^{-4} M, was added to each preparation to assess whether any tension changes resulted. To assess whether BAY u3405 was a bronchodilator, guinea-pig tracheal rings were contracted with carbachol and increasing concentrations of BAY u3405 added up to 10^{-4} M. Isoprenaline (10^{-6} M) was then added to determine the maximal relaxant response.

Data analysis

Data were expressed as arithmetic or geometric means with 95% confidence limits. Student's *t* test was used for paired, or unpaired, data as appropriate. Linear regression was employed to calculate EC_{50} values. Dose-ratios were calculated from the ratio of EC_{50} values for the test agonist. The method of Arunlakshana & Schild (1959) was used to determine pA_2 values. The pA_2 values were calculated with the slope constrained to unity after linear regression had shown the slope not to be significantly different from unity. If a parallel shift of the agonist concentration-response curve was only observed at a single antagonist concentration a $pK_B = \log$ (dose ratio $-$ 1)/[antagonist]) was determined at that concentration.

Drugs

BAY u3406 and BAY u3405 (respectively 3(S) and 3(R)-[[(4-fluorophenyl)sulphonyl]amino-1,2,3,4-tetrahydro-9H-carbazole-9-propanoic acid]) were supplied by Dr U. Rosentreter (Institute of Chemistry, Bayer AG, Wuppertal, Germany). Stock solutions of 10^{-2} M were prepared by dissolving BAY u3405 or u3406 in dimethylsulphoxide and serial dilutions were prepared in phosphate-buffered saline. Other drugs were dissolved as previously described.

Drugs were obtained from the following suppliers:— PGD_2, 16,16-dimethyl- PGE_2, U46619 (11α,9α-epoxymethano- prosta-5Z,13E-dienoic acid) PGI_2, carbachol, indomethacin, isoprenaline and 5-hydroxytryptamine (Sigma); LTC_4 and LTD_4 (Dr T.S. Abram, Bayer UK, Bucks); 9α,11β-PGF_2 (Salford Ultrafine Chemicals, Manchester), I-BOP ((1S-[1α,2α(Z), 3β(1E,3S,5S)4α])-7-(3-[3-hydroxy-4-{4-iodophenoxy}-1-butenyl]-7-oxabicyclo [2,2,1]hept-2-yl)-5-heptenoic acid) (Cayman Chemicals, Ann Arbor, MI, U.S.A.). $PGF_{2\alpha}$ (Medimpex, Budapest, Hungary), butaprost (methyl (11α, 13(E),16(S))-11,16-dihydroxy-9-oxo-17,17-(spirobutyl)prosta-13-enoate) (Bayer AG), fluprostenol (5Z, 11α, 13E,15(S))-11,15-dihydroxy 16-(3-trifluromethylphenoxy)-17,18,19,20-tetranor-9-oxo prosta-5,13-dienoic acid (ICI, Macclesfield, Cheshire), GR32191 ((Z)-1(R), 2(R), 3(S), 5(S))-7-[5-(biphenyl-4-ylmethoxy)-3-hydroxy-2-piperidinocyclopentyl]hept-4-enoic acid hydrochloride) (Glaxo, Ware, Herts.) and BW245C (5-(6-carboxyhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin) (Wellcome, Beckenham, Kent). All salts used were of AnalaR grade.

Results

Intrinsic activity

BAY u3405 at concentrations between 10^{-9} M and 10^{-4} M in the presence, or absence, of indomethacin had no direct contractile effect on the airway smooth muscle of any of the species examined. Guinea-pig and human airways were examined in the presence or absence of indomethacin, whilst rat and ferret airways were examined solely in the presence of indomethacin. On human airway tissue, small reductions in tone were often observed but did not appear to be dose-related, although a small relaxation was consistently observed at 10^{-4} M. Against carbachol-induced tone on guinea-pig trachea, BAY u3405 (10^{-6} to 10^{-4} M) produced a small dose-related relaxation (20% of the isoprenaline maximum at 10^{-4} M BAY u3405).

Antagonism at thromboxane A_2 receptors

BAY u3405 produced rightward shifts in the U46619 concentration-response curves in airway smooth muscle from all four species examined. The effects of BAY u3405 were examined over at least a hundred fold concentration range, between 10^{-9} and 10^{-6} M, and produced progressive, concentration-related, displacements of the U46619 concentration-response curves (Figures 2 and 3). Schild analysis indicated that, in each case, the slope of the regression line did not differ significantly from unity (Table 1) and the pA_2 values were then calculated (Table 1). Similarly when another TXA_2 mimetic, I-BOP, was used as the agonist

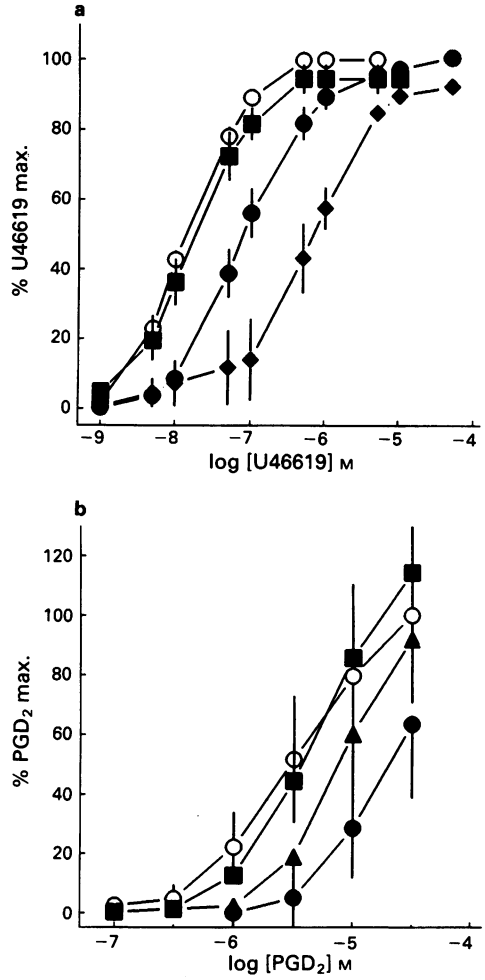

Figure 2 The effect of BAY u3405 on contractions of guinea-pig trachea induced by (a) U46619; control (○); BAY u3405 10^{-9} M (■), 10^{-8} M (●) and 10^{-7} M (◆). Mean from 6 preparations; vertical lines show s.e.mean; and (b) PGD_2; control (○); BAY u3405 10^{-9} M (■), 3×10^{-9} M (▲) and 10^{-8} M (●). Mean from 8 preparations; vertical lines show s.e.mean.

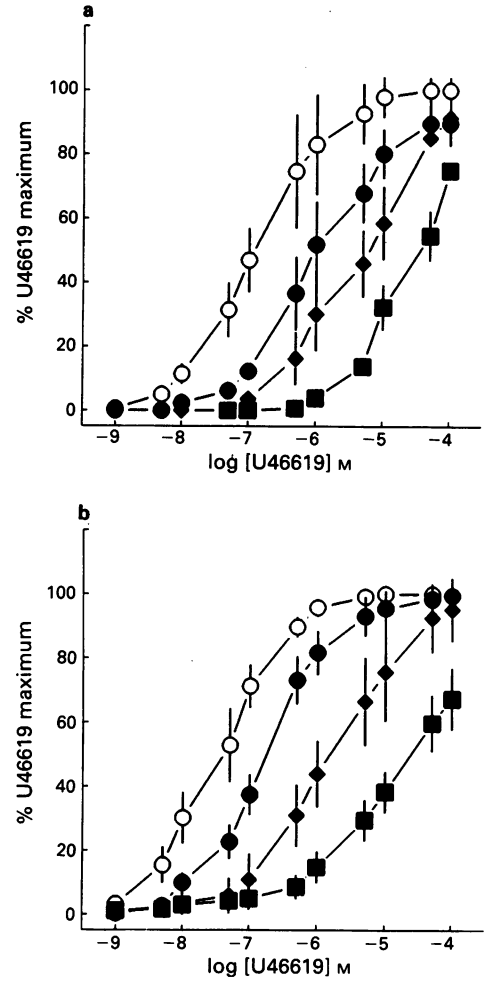

Figure 3 The effect of BAY u3405 on U46619-induced contractions of (a) human lung strip and (b) human bronchial muscle. U46619: control (○); BAY u3405 10^{-8} M (●), 10^{-7} M (◆) and 10^{-6} M (■): mean from 4 preparations; vertical lines show s.e.mean.

on guinea-pig lung strip, BAY u3405 was found to behave as a competitive antagonist (Figure 4).

Other prostanoids also contract airway smooth muscle via activation of TXA_2 receptors, generally with a maximal response markedly less than that of U46619 (McKenniff *et al.*, 1988; 1989). Contractile responses, to these prostanoids, of human and ferret airway smooth muscle were essentially abolished in the presence of 10^{-6} M BAY u3405 (Table 2). Only with the guinea-pig tissues was it possible to show competitive antagonism consistent with the Schild equation. BAY u3405 competitively antagonized contractions of guinea-pig trachea induced by PGD_2 (Figure 2) or its metabolite 9α, 11β-PGF_2. Similarly, on guinea-pig lung strip it acted as a competitive antagonist of contractions induced by PGD_2 (Figure 4) and abolished, the smaller, contractions induced by $PGF_{2\alpha}$ and 9α, 11β-PGF_2 (Table 2).

BAY u3405 and GR32191 were compared on three preparations against U46619 at an antagonist concentration of 10^{-7} M. On guinea-pig trachea both compounds gave a mean pK_B of 8.8 (data not shown). On both human bronchial muscle and rat lung strip a smaller shift in the U46619 concentration-response curve was observed in the presence of GR32191 than BAY u3405 (Figure 5). In these experiments the mean pK_B for BAY u3405 was 8.4 on both preparations whereas GR32191 gave pK_B values of 6.9 on rat lung strip and 7.7 on human bronchial muscle.

Table 1 The potency of BAY u3405 against U46619-induced contractions of respiratory smooth muscle

Tissue	pA_2	*Slope*	n
Human bronchial muscle	8.8 ± 0.3	1.15 ± 0.38	4
Human lung strip	8.9 ± 0.3	0.88 ± 0.13	4
Ferret tracheal ring	8.1 ± 0.3	1.09 ± 0.19	4
Guinea-pig tracheal ring	8.7 ± 0.2	0.78 ± 0.27	6
Guinea-pig lung strip	8.1 ± 0.3	1.09 ± 0.40	6
Rat lung strip	8.6 ± 0.1	0.70 ± 0.34	6

Data are shown as the mean ± 95% confidence limits from *n* preparations.

Selectivity

Non-prostanoids BAY u3405 (10^{-6} M) had no effect on the guinea-pig trachea against any of the following non-prostanoid agonists: carbachol, histamine, 5-hydroxytryptamine, LTC_4, LTD_4 or isoprenaline, nor against LTD_4 on human lung strip or carbachol on rat lung strip. Even 10^{-5} M BAY u3405 had no effect against histamine or LTD_4 on guinea-pig trachea (this concentration was not tested against other agonists).

Prostanoids The lack of affinity of BAY u3405 for other prostanoid receptor types was demonstrated by the absence of an effect of BAY u3405 (10^{-6} M) at the following prostanoid receptor types:— DP (PGD_2 and BW245C on rabbit jugular vein); EP_1 (16,16-dimethyl-PGE_2 and $PGF_{2\alpha}$ on guinea-pig

Table 2 The potency of BAY u3405 against prostanoid-induced contractions of respiratory smooth muscle

Tissue	*Agonist*	pK_B	pA_2	n
Guinea-pig trachea	PGD_2		8.6 ± 0.2[a]	8
	$9\alpha,11\beta$-PGF_2		9.1 ± 0.3[a]	4
	$PGF_{2\alpha}$	<5		4
	16,16-dimethyl-PGE_2	<5		4
Guinea-pig lung strip	PGD_2	8.9 ± 0.8[b]		6
	$PGF_{2\alpha}$	>8[c]		4
	I-BOP		7.8 ± 0.1[a]	4
Human lung strip	16,16-dimethyl-PGE_2	>8[d]		4
	PGD_2	>8[d]		4
	$PGF_{2\alpha}$	>8[d]		4
Human bronchial muscle	16,16-dimethyl-PGE_2	>8[d]		3
	PGD_2	>8[d]		1
	$PGF_{2\alpha}$	>8[d]		1
Ferret tracheal ring	16,16-dimethyl-PGE_2	>8[c]		4

[a] From Schild analysis, mean ± 95% confidence limits. The slopes were not significantly different from unity.
[b] In the presence of 10^{-8} M BAY u3405. Geometric mean ± s.e.mean.
[c] No contractile response observed in the presence of 10^{-7} M BAY u3405.
[d] No contractile response observed in the presence of 10^{-6} M BAY u3405.
For abbreviations, see text.

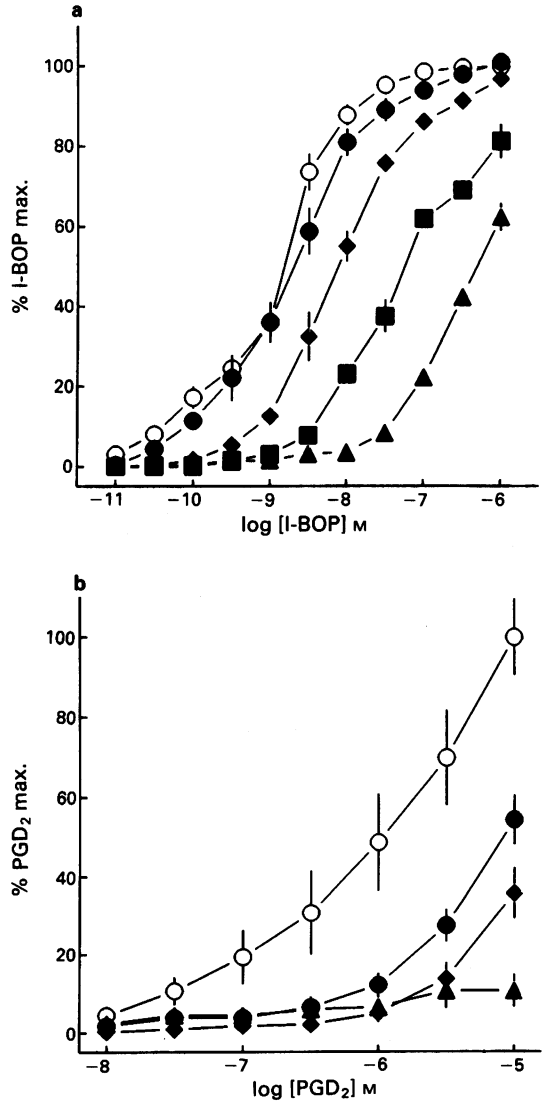

Figure 4 The effects of BAY u3405 on contractions of guinea-pig lung strip induced by (a) I-BOP: control (○); BAY u3405 10^{-8} M (●), 10^{-7} M (◆), 10^{-6} M (■) and 10^{-5} M (▲). Points are the mean from 4 preparations. (b) PGD_2: control (○); BAY u3405 10^{-8} M (●); 3×10^{-8} M (◆) and 3×10^{-7} M (▲). Points are the mean from 6 preparations. Vertical lines show s.e.mean in both (a) and (b).

trachea); EP_2 (butaprost on guinea-pig trachea); FP ($PGF_{2\alpha}$ and fluprostenol on rat colon); IP (PGI_2 on rabbit jugular vein).

Stereoselectivity Since BAY u3405 is a chiral antagonist we also evaluated the ability of its enantiomer BAY u3406 to

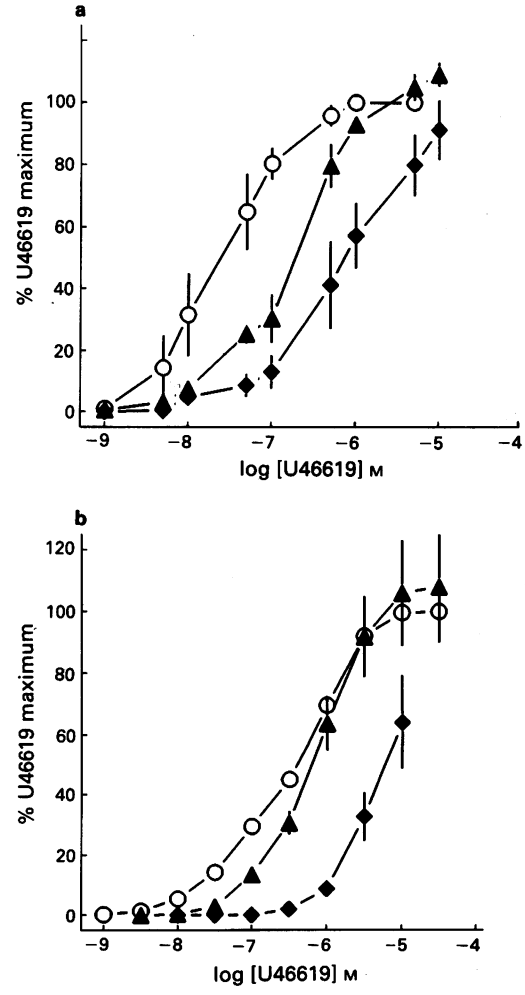

Figure 5 Comparison of the effect of 10^{-7} M BAY u3405 (◆) and 10^{-7} M GR32191 (▲) against U46619 control (○) on (a) human bronchial muscle and (b) rat lung strip. Mean from 4 preparations; s.e.mean shown by vertical lines.

Table 3 The potency of BAY u3405 against U46619-induced contractions of airway smooth muscle

Tissue	pK_B	n
Guinea-pig trachea	7.1 ± 0.2[a]	6
Human lung strip	6.6, 7.2[b]	2
Human bronchial muscle	6.7, 7.3[b]	2

[a] Geometric mean ± s.e.mean in the presence of 10^{-6} M BAY u3406.
[b] Observed values.

antagonize U46619-induced contractions of a number of preparations (Table 3). In each case this compound only produced a significant shift in the U46619 concentration-response curve at the highest concentration tested (10^{-6} M) from which pK_B values were calculated.

Discussion

We have shown BAY u3405 to be a potent TXA_2 receptor antagonist on airway smooth muscle preparations from a range of species including man. On no occasion was any inherent contractile activity observed with BAY u3405 on any of the tissues studied. The high potency of this drug on human airways suggests that it will be an ideal tool to elucidate the role of the TXA_2 receptor in airway diseases such as asthma.

BAY u3405 is a competitive antagonist of TXA_2 receptors. On all of the tissues studied it produced a parallel concentration-related rightward shift of the U46619 concentration-response curve with no suppression of the maximal response. The antagonism was surmountable and slopes of the Schild plots did not differ significantly from unity.

BAY u3405 was a selective TXA_2 antagonist. It had no effect on contractile responses induced by non-prostanoids at concentrations which were approximately three orders of magnitude greater than those shown to be effective against U46619. Similarly, when evaluated against selective agonists for each receptor, on a selection of tissues reported to possess a homogeneous or predominant population of each prostanoid receptor, BAY u3405 was inactive as an antagonist. We and others have previously found that on some airway preparations PGD_2, its metabolite 9α, 11β-PGF_2, and 16,16- dimethyl-PGE_2 induce contractile responses through TXA_2 receptors (McKenniff *et al.*, 1988; Featherstone *et al.*, 1990). It was not surprising therefore to find that BAY u3405 was a potent antagonist of these prostanoids on tissues where they were purported to activate TXA_2 receptors. On other tissues, such as the guinea-pig trachea where $PGF_{2\alpha}$ and 16,16-dimethyl-PGE_2 induce contractions via EP_1 receptors, BAY u3405 was inactive against such effects (McKenniff *et al.*, 1988).

Evidence from a number of studies points to the existence of TXA_2 receptor subtypes. However, from the available evidence it is uncertain how many subtypes exist. Mais *et al.* (1988) found a difference in rank orders of potency with a series of azapinane TXA_2 antagonists evaluated on both human platelets and canine saphenous vein. In an extensive study using both platelets and smooth muscle from three species Tymkewycz *et al.* (1991) concluded that variations in antagonist affinity could only be explained by the existence of TXA_2 receptor subtypes.

We have recently described differences in antagonist affinity on rat and guinea-pig lung strips as further evidence for TXA_2 receptor heterogeneity (Cuthert *et al.*, 1991). In the present studies it would appear that BAY u3405 displayed little selectivity between such subtypes. Human bronchial muscle, human lung strip and rat lung strip are probably the best airway preparations to demonstrate this point. Although most TXA_2 antagonists are effective on human lung strip they have markedly reduced potencies on the rat lung strip and human bronchial muscle (Cuthbert *et al.*, 1991, and unpublished observations). In contrast, however, BAY u3405 had comparable activity on all three tissues. We investigated this point further by comparing BAY u3405 with GR32191 on both human bronchial muscle and rat lung strips under identical conditions to those described in the present BAY u3405 studies (Figure 5). The potency of GR32191 on both these tissues was markedly less than that reported by Lumley *et al.*, (1989) on a range of TXA_2 receptor systems. Our results, on both rat lung and guinea-pig trachea were comparable to those reported. In contrast BAY u3405 had comparable activity on both tissues similar to that on human lung strip and a wide range of non-airway tissues. Thus although distinct TXA_2 receptor subtypes may exist, as suggested by the results with GR32191, BAY u3405 displays little, or no, subtype selectivity.

On some tissues, however, BAY u3405 did have a lower potency than expected against TXA_2-mimetics but not PGD_2 or $PGF_{2\alpha}$. On the guinea-pig lung strip where TXA_2 receptors are reported to be predominant, this drug was approximately one order of magnitude weaker against U46619 or another TXA_2-mimetic (I-BOP) than normally observed. Whilst this might be explained by the presence of a heterogeneous population of TXA_2 receptors neither we (McKenniff *et al.*, 1988) nor others (Coleman *et al.*, 1990) have observed, using a range of TXA_2 antagonists against U46619 concentration-response curves, Schild plots with slopes significantly different from unity or obtained pA_2 values on this tissue that differ markedly from those on the guinea-pig trachea. Even against I-BOP, where BAY u3405 was employed over a 1000 fold concentration range, there was no indication that the slope of the Schild plot deviates from unity (slope 0.96 ± 0.14). However, it is possible to observe linear Schild plots in heterogeneous systems (Kenakin, 1987).

The U46619 concentration-response curve on guinea-pig lung is shallow (spanning four orders of magnitude) possibly suggestive of the presence of two TXA_2 receptor types. If two receptor types are present then it would be anticipated that an antagonist might give different pA_2 values against different agonists. The low potency and efficacy of PGD_2 (Figure 4) make it difficult to obtain Schild plots. Only in the presence of 10^{-8} M BAY u3405 did the PGD_2 concentration-response curve reach its own EC_{50} level. This resulted in a large variation in observed pK_Bs. Thus any difference in the observed affinities of BAY u3405, against the three agonists employed, is probably apparent rather than real. To ascertain whether this preparation contains two subtypes would require evaluation of an antagonist against a wider range of agonists.

It has been shown that substantial quantities of both TXA_2 and PGD_2 are produced in the lung upon allergen challenge in asthmatics (Wenzel *et al.*, 1989). However it remains unresolved at present whether TXA_2 receptors play a significant role in airway diseases. As yet GR32191 is the only TXA_2 antagonist reported to have been evaluated against both PGD_2 and allergen challenge in man (Beasley *et al.*, 1989). Its activity against both challenges was modest and has not resolved this problem. While this result may be due to factors other than receptor affinity it is tempting to speculate that the limited profile of TXA_2 antagonism of GR32191 on airway preparations, as shown in this paper diminishes its value as a drug tool to clarify this area. In contrast BAY u3405 has a good profile at all TXA_2 subtypes especially in human tissue, suggesting that it is the ideal drug tool for investigating TXA_2 receptors in airway disease.

In summary, BAY u3405 is a potent, competitive and selective TXA_2 receptor antagonist on a range of airway smooth muscle including human. Such activity coupled with good oral potency and duration of action in the guinea-pig (Francis *et al.*, 1991) and tolerance in man (Weber *et al.*, 1990) suggest that BAY u3405 is the most promising drug tool for clinical investigation of the role of TXA_2 and prostanoids (e.g. PGD_2) which act through TXA_2 receptors in airway disease, most notably asthma.

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