ELSEVIER

European Journal of Pharmacology 354 (1998) 173–178

ejp

Interspecies differences in thromboxane A_2 receptors are distinguished by glibenclamide

Barbara K. Kemp, Grant A. McPherson *

Department of Pharmacology, Monash University, Clayton 3168, Victoria, Australia

Received 2 April 1998; revised 5 June 1998; accepted 12 June 1998

Abstract

The ability of the thromboxane A_2 receptor antagonist, GR32191 ([1*R*-[1α(*Z*),2β3β,5α]]-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid), and the sulphonylurea, glibenclamide, to antagonise contractions to the thromboxane A_2 mimetic, U46619 ((15*S*)-hydroxy-11α,9α(epoxymethano)prosta-5*Z*, 13*E*-dienoic acid), were assessed in rat and guinea-pig isolated large (aorta) and small (mesentery and coronary) arteries. U46619 concentration–response curves were constructed in the absence and presence of GR32191 and glibenclamide and pK_B values calculated. GR32191 caused significant rightward shifts in U46619 concentration–response curves and was a more potent antagonist in guinea-pig vessels ($pK_B \sim 9.4$) than rat arteries ($pK_B \sim 7.9$). Conversely, glibenclamide failed to inhibit contractions to U46619 in guinea-pig vessels but antagonised responses to U46619 in rat aorta ($pK_B = 6.1$) and mesenteric artery ($pK_B = 6.3$). In combination, GR32191 and glibenclamide caused a shift in the concentration–effect curve to U46619 in rat aorta that was additive. These results suggest that glibenclamide can discriminate between species differences in thromboxane A_2 receptors and may exert its inhibitory effect upon U46619-mediated contractions at the level of the thromboxane A_2 receptor.

Keywords: Sulphonylurea; Thromboxane A_2; U46619; GR32191; Mesenteric artery; Coronary artery; Aorta

1. Introduction

It is well recognised that sulphonylureas, such a glibenclamide, block ATP-sensitive K^+ channels (K_{ATP}; Challinor-Rogers and McPherson, 1994). In 1990, however, an additional action of glibenclamide was discovered in that it was found to competitively antagonise contractions to the thromboxane A_2 mimetic, U46619 ((15*S*)-hydroxy-11α,9α(epoxymethano)prosta-5*Z*, 13*E*-dienoic acid), in canine isolated coronary arteries (Cocks et al., 1990). Subsequent studies have demonstrated an ability of glibenclamide and other sulphonylureas to antagonise responses to U46619 and other prostanoids in vessels from the rabbit (Nielsen-Kudsk and Thirstrup, 1991), rat (Delaey and Van de Voorde, 1995, 1997), pig (McPherson et al., 1997), cow (Delaey and Van de Voorde, 1997) and human (Stanke et al., 1998). To date, the mechanism via which sulphonylureas block the response to prostanoids remains unclear. It has been suggested, however, that sulphonylureas may interfere with the signal transduction process of prostanoid receptors, possibly at the level of the G-protein (Delaey and Van de Voorde, 1995). In addition, the ability of sulphonylureas to antagonise prostanoid responses is not conserved among all species. Thus, Delaey and Van de Voorde (1997) found that in contrast to the rat, glibenclamide did not impair U46619-mediated contraction in guinea-pig isolated aorta or carotid artery.

Interestingly, differences between rat and guinea-pig smooth muscle thromboxane-A_2 prostanoid (thromboxane) receptors have been identified (Ogletree and Allen, 1992; Zhang et al., 1996). This conclusion was drawn from data which showed a different rank order of potency for a number of structurally related U46619 antagonists in the two species. Taken together with the glibenclamide data, this finding suggests that glibenclamide may also be able to discriminate between thromboxane receptors in rat and guinea pig. One purpose of this study was to test this hypothesis directly. In addition we examined whether the inhibitory influence of sulphonylureas upon prostanoid receptors is also apparent in small, resistance-like arteries.

* Corresponding author. Tel.: +61-3-9905-4856; Fax: +61-3-9905-5851; E-mail: grant.mcpherson@med.monash.edu.au

0014-2999/98/$19.00

A recent finding that glibenclamide antagonised responses to U46619 in human isolated internal mammary artery and saphenous vein (Stanke et al., 1998) but not in human isolated small subcutaneous arteries (Delaey and Van de Voorde, 1997) suggests that the ability of glibenclamide to inhibit thromboxane receptors may not be conserved in resistance-like arteries. Lastly we performed functional experiments to determine whether glibenclamide and the thromboxane receptor antagonist, GR32191 ([1*R*-[1α(*Z*),2β3β,5α]]-7-[5-[[(1,1′-biphenyl)-4-yl]methoxy]-3-hydroxy-2-(1-piperidinyl)cyclopentyl]-4-heptenoic acid) (Lumley et al., 1989), interact at the same site to antagonise contractions to U46619. In order to achieve this and other objectives we have examined the ability of glibenclamide and GR32191 to antagonise contractions to U46619 both alone and in combination, in rat and guinea-pig isolated large (aorta) and small (coronary and mesenteric) arteries.

2. Materials and methods

2.1. Isolation and study of arterial segments

Male Wistar Kyoto (WKY) rats were killed via CO_2 asphyxia and male Duncan–Hartley guinea-pigs via cervical dislocation. Segments of small mesenteric artery, corresponding to a third or fourth order branch from the superior mesenteric artery and the thoracic aorta, were obtained from the rat. Left anterior descending coronary artery and the thoracic aorta were obtained from the guinea pig. The vascular segments were rapidly removed and placed in ice cold Krebs' solution (composition in mM: NaCl 119, KCl 4.7, $MgSO_4$ 1.17, $NaHCO_3$ 25, KH_2PO_4 1.18, $CaCl_2$ 2.5 and glucose 5.5) pH 7.4 and gassed with carbogen (95% O_2, 5% CO_2).

Segments (2 mm) of small arteries (rat mesenteric and guinea-pig coronary) were mounted in a small vessel myograph as previously described (McPherson, 1992). Briefly, two 40 μm wires were threaded through the lumen of the vessel segment. One wire was attached to a stationary support driven by a micrometer, while the other was attached to an isometric force transducer. The endothelium was removed mechanically from all small arteries using a polyethylene suture (6/0 prolene, Ethicon) as previously described (McPherson and Angus, 1991). Segments (4 mm) of aorta (rat and guinea pig) were mounted on 400 μm wires in a large vessel myograph as previously described (McPherson et al., 1997). The endothelium was removed by rubbing the luminal surface with a wooden probe. In all arteries, the absence of endothelium was confirmed by ensuring the absence of response to acetylcholine (1 μM).

All vessels were allowed to equilibrate under zero force for 30 min in 37°C Krebs' solution. Using the diameter of the vessel, calculated from the distance between the two mounting wires, a passive diameter–tension curve was constructed as previously described (Mulvany and Halpern, 1977; see McPherson, 1992 for details). From this curve the effective transmural pressure was calculated. The vessel was then set at a tension equivalent to that generated at 0.9 times the diameter of the vessel at 100 mmHg. The diameters of rat mesenteric and guinea-pig coronary arteries at an equivalent transmural pressure of 100 mmHg (D_{100}) were approximately 350 and 400 μm, respectively. The diameters of rat and guinea-pig aorta, at an equivalent transmural pressure of 100 mmHg (D_{100}), were approximately 3000 μm.

After another 30 min, vessels were contracted with K^+ depolarising solution (KPSS, composition in mM: KCl 123, $MgSO_4 \cdot 7H_2O$ 1.17, KH_2PO_4 2.37, $CaCl_2$ 2.5, EDTA 0.026 and glucose 5.5). Once the KPSS-induced contraction had reached a plateau, the tissues were washed and the force allowed to return to baseline. Data were captured by the use of the CVMS data acquisition system (Version 2.0, World Precision Instruments, USA).

2.2. U46619 responses in rat mesenteric and guinea-pig coronary artery

Preliminary studies demonstrated time-dependent changes in the concentration–response curves to U46619 in both rat mesenteric and guinea-pig coronary artery. In rat mesenteric artery, the third consecutive concentration–response curve to U46619 was found to be the most reproducible and was therefore used as the control response in all studies. Similarly, the second concentration–response curve to U46619 was used as the control response in guinea-pig coronary artery. Prior to construction of each U46619 concentration–response curve in guinea-pig coronary artery, vessels were exposed twice to high K^+ (55 mM) isotonic Krebs' solution for 5 min. Ten minutes were allowed to elapse between each addition of 55 mM K^+. Following construction of the first concentration–response curve to U46619 in both rat mesenteric and guinea-pig coronary arteries, acetylcholine (1 μM) was added to confirm the absence of the endothelium.

In a group of rat mesenteric arteries and guinea-pig coronary arteries, glibenclamide (10 μM) or GR32191 (0.3 μM—mesenteric, 3 nM—coronary) were added 30 and 60 min, respectively, prior to construction of a concentration–response curve to U46619. In rat mesenteric arteries glibenclamide was added between the 2nd and 3rd U46619 concentration–effects curve while in guinea-pig coronary arteries glibenclamide and GR32191 were added between the 1st and 2nd U46619 concentration–effect curves.

2.3. U46619 responses in rat and guinea-pig aorta

Aorta were initially precontracted to approximately 50% of their maximum contraction to KPSS with phenyl-

ephrine. Once the phenylephrine contraction had reached a stable plateau, acetylcholine (1 μM) was added to test for the functional removal of the endothelium. Following this procedure, aorta were thoroughly washed and force allowed to return to baseline.

Subsequently, concentration–response curves to U46619 were constructed in either the absence or presence of glibenclamide (10 μM) and GR32191 (0.3 μM—rat aorta, 3 nM—guinea-pig aorta) alone or in combination (see Section 2.4). Glibenclamide and GR32191 were added 30 and 60 min, respectively, prior to the addition of U46619. Only one concentration–response curve was obtained in any one ring of aorta.

2.4. The interaction between GR32191 and glibenclamide against U46619 mediated contractile responses

We wished to test the idea that GR32191 and glibenclamide were acting at the same site to cause their antagonism of U46619. To test the hypothesis functionally we employed the Paton and Rang test (1965; see Challinor and McPherson, 1993). This test is based on the following hypothesis. If two antagonists act at the same site, and are present simultaneously, the concentration-ratio of the two antagonists when combined, will be essentially additive (Eq. (1)).

$$CR_{2+1} = CR_1 + CR_2 - 1 \quad (1)$$

where CR_1 and CR_2 are the concentration-ratios for antagonist one and two, respectively, when assessed alone. CR_{2+1} is the concentration-ratio if both antagonists are present at the same time.

However, if the antagonists act at different sites, the expected concentration-ratio will be equal to the concentration-ratio of the first antagonist multiplied by the concentration-ratio of the second antagonist.

$$CR_{2+1} = CR_1 \cdot CR_2 \quad (2)$$

Four vascular segments were thus set up in parallel for these studies. A vessel acted either as a control, was treated with a single antagonist, or was treated with two antagonists simultaneously. Tissues were allocated randomly to the different treatment groups. Thus, in this series of experiments U46619 mediated contractile responses were obtained in the absence of any antagonist, in the presence of GR32191 (0.3 μM) alone, glibenclamide (10 μM) alone and GR32191 (0.3 μM) plus glibenclamide (10 μM) combined. Concentration-ratios were calculated as described below.

2.5. Data analysis

Contractile responses to U46619 were expressed as a percentage of the maximum contraction to KPSS (%KPSS). Computer estimates of the concentration of U46619 required to cause 50% of the maximum vasoconstrictor response (EC_{50}) was calculated using Graphpad Prism (version 2) and expressed as pEC_{50} ($-\log EC_{50}$).

Antagonist potency of glibenclamide and GR32191 was calculated using Eq. (3) which gives an estimate of antagonist potency based on a single concentration of antagonist (see Kenakin, 1987). Previous studies have shown that glibenclamide (Cocks et al., 1990) and GR32191 (Ogletree and Allen, 1992) are classical competitive antagonists of U46619 and consequently their calculated potency value (pK_B) would be independent of the concentration of antagonist used.

$$pK_B = -\log([\text{antagonist concentration, M}] / [\text{concentration ratio} - 1]) \quad (3)$$

Concentration-ratio (CR) = EC_{50} for agonist in the presence of antagonist/EC_{50} in the absence of antagonist.

Comparisons of pEC_{50} and maximum contraction values between control, glibenclamide and GR32191 treated arteries were performed using one way analysis of variance (ANOVA). If the F statistic exceeded the critical value, then Dunnett's modified t-statistic was used to make comparisons between the control and treatment groups.

For statistical comparison, concentration-ratios calculated from the EC_{50} values were first converted to logarithm values but are shown in the text as anti-logarithms. Multiple comparisons of pK_B values and concentration-ratios were made using a one-way ANOVA and Bonferonni's t-test. Results are expressed as mean ± S.E.M. and statistical significance was accepted at the $P < 0.05$ level.

2.6. Drugs

Drugs and their sources were: U46619 (The Upjohn, Kalamazoo, USA); glibenclamide, acetylcholine bromide, L-phenylephrine hydrochloride (Sigma, St. Louis, USA); GR32191 (Glaxo, UK). Stock solutions of U46619 (1 mM) were made up in absolute ethanol, glibenclamide (10 mM) in dimethyl sulphoxide (DMSO) and GR32191 (10 μM) in distilled water. All subsequent dilutions were in distilled water.

3. Results

3.1. Antagonism of U46619 responses by GR32191 and glibenclamide

The ability of GR32191 and glibenclamide to antagonise U46619 responses in rat and guinea-pig arteries were compared. U46619 caused concentration-dependent contractions in rat isolated aorta ($pEC_{50} = 8.62 \pm 0.08$, 127 ± 11% KPSS; $n = 5$, Fig. 1A) and mesenteric artery (pEC_{50}

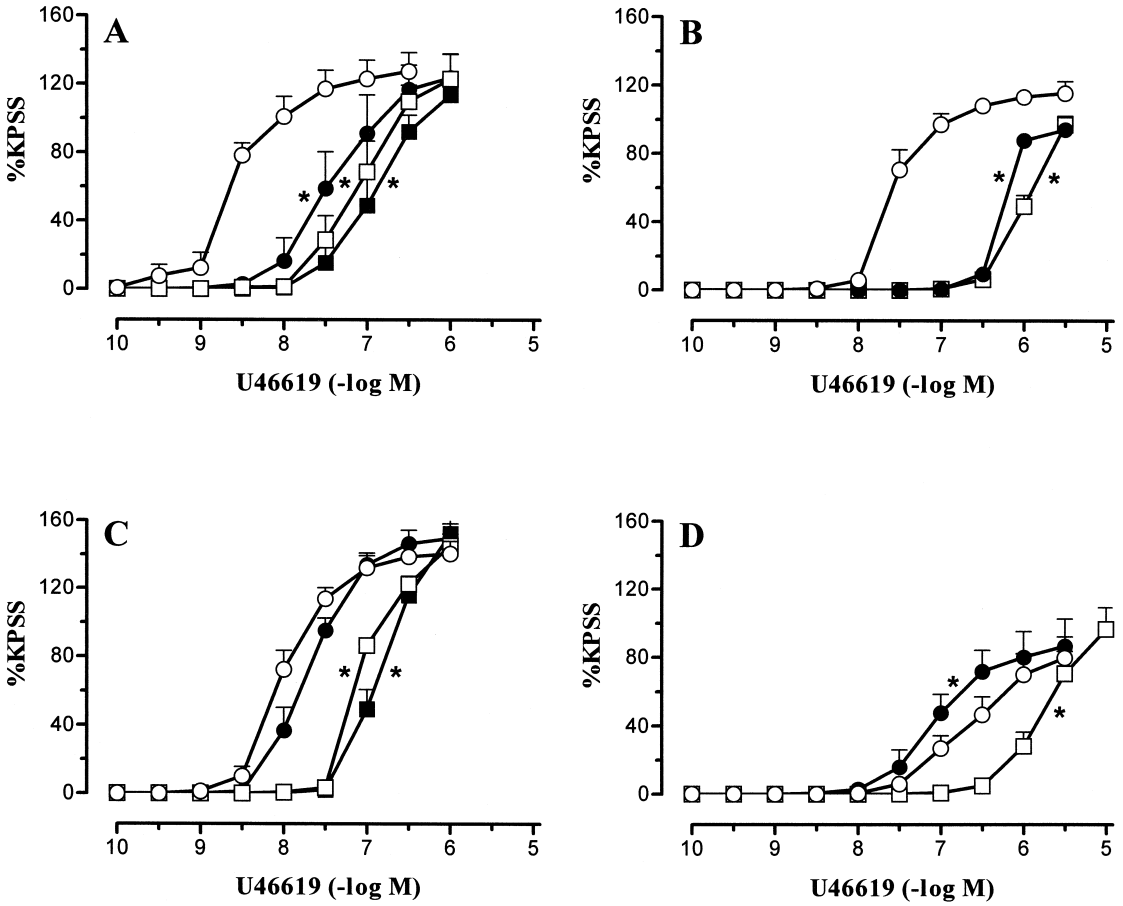

Fig. 1. Concentration–response curves to U46619 in rat isolated thoracic aorta (A) and mesenteric artery (B) and guinea-pig isolated thoracic aorta (C) and left anterior descending coronary artery (D). Curves were obtained in the absence (control, ○) and presence of glibenclamide (●), GR32191 (□) and glibenclamide and GR32191 in combination (■). A and B: glibenclamide tested at 10 μM, GR32191 tested at 0.3 μM. C and D: glibenclamide tested at 10 μM, GR32191 tested at 3 nM. Values are mean ± S.E.M. $*pEC_{50}$ value significantly different from control ($P < 0.05$, Dunnett's modified *t*-test).

$= 7.52 \pm 0.10$, $113 \pm 3\%$ KPSS; $n = 6$, Fig. 1B). In both aorta and mesenteric artery, glibenclamide (10 μM) and GR32191 (0.3 μM) caused significant right-ward shifts in the concentration–response curves to U46619, with little change in maximum response (Fig. 1A and B). The calculated pK_B values for both glibenclamide and GR32191 in rat arteries are given in Table 1. Glibenclamide ($pK_B \sim 6.2$) was approximately 50-fold less potent than GR32191 ($pK_B \sim 7.95$) in both the aorta and mesenteric artery.

In contrast to findings in rat arteries, glibenclamide (10 μM) failed to antagonise the response to U46619 in the guinea-pig aorta (pEC_{50} control $= 8.02 \pm 0.08$, $140 \pm 7\%$ KPSS, $n = 5$; pEC_{50} glibenclamide $= 7.70 \pm 0.09$, $150 \pm 9\%$ KPSS, $n = 5$; Fig. 1C). In the guinea-pig coronary artery, glibenclamide produced a small increase (3-fold) in the sensitivity to U46619 (pEC_{50} control $= 6.54 \pm 0.18$, $78 \pm 12\%$ KPSS, $n = 5$; pEC_{50} glibenclamide $= 7.07 \pm 0.08$, $87 \pm 16\%$ KPSS, $n = 4$; Fig. 1D). In contrast to glibenclamide, GR32191 was much more potent in the guinea pig than the rat (30-fold; pK_B guinea pig ~ 9.3 cf. rat ~ 7.9). Thus at a concentration of 3 nM, GR32191 caused a significant 9- and 7-fold decrease in the sensitivity to U46619 in guinea-pig aorta (Fig. 1C) and coronary artery (Fig. 1D), respectively, with no change in maximum contraction (Table 1). The ability of GR32191 to antagonise U46619 responses in guinea-pig aorta was unchanged in the presence of glibenclamide (10 μM, Fig. 1C).

Table 1
Mean pK_B values for glibenclamide and GR32191 against U46619 contractions in rat isolated thoracic aorta and mesenteric artery and guinea-pig isolated thoracic aorta and left anterior descending coronary artery

Artery	GR32191 (pK_B)	Glibenclamide (pK_B)
Rat		
Aorta	7.98 ± 0.11^a	6.13 ± 0.19
Mesenteric artery	7.91 ± 0.09^a	6.33 ± 0.07
Guinea pig		
Aorta	9.34 ± 0.12^b	< 5
Coronary artery	9.44 ± 0.25^b	< 5

Values are the mean ± S.E.M. from 4–5 separate determinations.
[a,b] Values marked with the same superscript were not significantly different ($P < 0.05$, Bonferroni's *t*-test).

Table 2
Concentration-ratios (CR) calculated for GR32191 (0.3 μM) and glibenclamide (10 μM) against U46619-induced contraction in the rat isolated thoracic aorta

Compound	CR alone	CR combined	Theoretical additive[c]	Theoretical multiplied[c]
GR32191 (0.3 μM)	30 (29–31)	47 (45–48)[a]	46 (44–47)[a]	447 (445–449)[b]
Glibenclamide (10 μM)	15 (13–16)			

Concentration-ratios were determined for each antagonist alone and in combination.
Concentration-ratios were converted to logarithms before averaging and statistical comparison. The results were then converted back for representation in this table.
The values in parentheses are ±S.E.M. calculated from the log (CR S.E.M.).
Mean values were calculated from 5 separate experiments.
[a,b] Values marked with the same superscript were not significantly different ($P < 0.05$, Bonferroni's *t*-test).
[c] The theoretical additive and multiplicative values were calculated from the individual concentration-ratios for each antagonist alone (Eqs. (1) and (2); see Section 2.4).

3.2. Interaction between GR32191 and glibenclamide in rat thoracic aorta

Experiments were performed to determine the concentration-ratio of GR32191 and glibenclamide alone and in combination. The results from these studies are shown graphically in Fig. 1A. Table 2 summarises the actual concentration-ratios calculated when the two antagonists were present alone and then in combination. Also presented in this table are theoretical 'additive' and 'multiplied' concentration-ratios calculated, using Eqs. (1) and (2), from the concentration-ratios of each antagonist when present alone. The actual concentration-ratio was statistically compared with the theoretical values to determine which model (additive or multiplicative) was most appropriate.

The combination of glibenclamide (10 μM) and GR32191 (0.3 μM) resulted in a concentration-ratio of approximately 47 (Table 2). This value compares favourably with the theoretical value obtained when the concentration-ratios for each antagonist alone were added (concentration-ratio = 46) rather than when multiplied (concentration-ratio = 447) (Table 2).

4. Discussion

Interspecies differences in thromboxane receptors have previously been identified. Specifically, the rank order of potency of a range of competitive antagonists of thromboxane receptors has been found to differ between rat and guinea-pig vessels (Ogletree and Allen, 1992; Zhang et al., 1996) therefore suggesting that rat and guinea-pig thromboxane receptors are pharmacologically and, perhaps, structurally different. The main finding from this study is that glibenclamide also discriminates between these species differences in thromboxane receptors. Thus, in the rat where GR32191 is relatively less potent ($pK_B \sim 7.9$), the thromboxane receptor is glibenclamide-sensitive, whereas in the guinea pig, where GR32191 is very potent ($pK_B \sim 9.3$), glibenclamide does not antagonise U46619 responses. Further work is required to determine if this relationship between high GR32191 potency and glibenclamide insensitivity is conserved among other species and vessels in which prostanoid-mediated contractions are resistant to sulphonylureas, such as human subcutaneous arteries (Delaey and Van de Voorde, 1997).

In order to determine if the apparent structural modification of the thromboxane receptor that yielded GR32191 more potent in the guinea-pig than in the rat also altered the susceptibility of the receptor to antagonism by sulphonylureas, we compared the ability of glibenclamide to antagonise contractions to U46619 in rat and guinea-pig vessels. Glibenclamide failed to block contractions to U46619 in either guinea-pig aorta or coronary artery but antagonised responses to U46619 in rat aorta ($pK_B = 6.1$) and mesenteric artery ($pK_B = 6.3$). The calculated pK_B value for glibenclamide as a U46619 antagonist in rat vessels ($pK_B \sim 6.2$) is similar to pA_2 and pK_B values calculated in dog ($pA_2 = 6.2$; Cocks et al., 1990) and pig ($pK_B = 6.3$; McPherson et al., 1997) coronary arteries. Furthermore, tetraphenylphosphonium, another K_{ATP} channel antagonist, which unlike glibenclamide is thought to block the K_{ATP} channel pore directly (McPherson and Piekarska, 1994), failed to affect the U46619 concentration–effect curve in either the rat or guinea-pig aorta (Kemp and McPherson, unpublished data). These findings concur with those previously reported by us in the pig isolated coronary artery (McPherson et al., 1997) and suggest that the inhibitory action of glibenclamide against U46619 in the rat is independent of its ability to block K_{ATP} channels.

The present study has also demonstrated that in the rat at least, the inhibitory effect of glibenclamide upon U46619-mediated contractions is present in both large conduit (aorta) and small resistance-like (mesentery) arteries. Thus, the ability of glibenclamide to antagonise U46619 responses does not appear to be dependent upon vessel size. These findings contrast those made in human blood vessels in which glibenclamide has been found to antagonise responses to U46619 in large isolated internal mammary arteries and saphenous veins (Stanke et al.,

1998) but not in small subcutaneous arteries (Delaey and Van de Voorde, 1997). Given, however, large and small human arteries were obtained from different patient groups, further investigation is required in order to determine if thromboxane receptors differ within the human vasculature.

Another issue which we wanted to address in this study was the site of action of sulphonylurea-based compounds. A recent work (Delaey and Van de Voorde, 1995) showed that sulphonylureas were antagonists of a number of prostanoids including thromboxane A_2, prostaglandin $F_{2\alpha}$ and prostaglandin E_2. Their work provided evidence that the site of the prostanoid antagonism may be at the level of the regulatory G-proteins since glibenclamide also antagonised constrictor responses to AlF_4, an agent which is thought to act by activating the G_α component which then acts on phospholipase C to cause phosphoinositide breakdown. Recent work by us (McPherson et al., 1997) provided some evidence to support the idea that the antagonism by sulphonylurea-based compounds of thromboxane mediated responses occurs at a site distant from the actual thromboxane receptor. However, on the basis of the results obtained in this study we now question whether this is the case. Thus, in a study designed to investigate the interaction between GR32191 and glibenclamide we found that, when combined, the two antagonists caused a shift in the concentration-effect curve to U46619 that was additive. This is consistent with the idea that the two chemically unrelated compounds compete for the same site to cause U46619 antagonism (Paton and Rang, 1965). Obviously much more work is required to confirm this idea.

5. Conclusion

The present findings suggest that thromboxane A_2 (U46619) can mediate contraction in vascular tissues through two distinct types of receptors that appear delineated along species lines—glibenclamide-sensitive and glibenclamide-insensitive thromboxane receptors. In addition, glibenclamide may act at the level of the thromboxane receptor to exert its inhibitory effect.

Acknowledgements

Dr. McPherson is a Senior Research Fellow of the NH and MRC. Their support is gratefully acknowledged.

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