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Heterogeneity of the inhibitory influence of sulfonylureas on prostanoid-induced smooth muscle contraction

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Abstract

In addition to their hypoglycemic influence, sulfonylureas have been reported to inhibit prostanoid-induced vasoconstriction. Using isometric tension measurements we investigated whether this inhibitory influence is exerted by different sulfonylureas in various types of blood vessels from different species and in other types of smooth muscle cells. It was found that in addition to glibenclamide and tolbutamide also gliclazide (1 mM) and tolazamide (1 mM) block contractions induced by prostaglandin $F_{2\alpha}$ and the thromboxane A_2 mimetic U-46619 in rat aorta, but not the contractions elicited by norepinephrine, serotonin or high potassium. Glibenclamide (10 μM) inhibits the prostaglandin $F_{2\alpha}$- and U-46619-induced contractions on rat tail, femoral and renal interlobar arteries and on bovine retinal and ciliary arteries, but not those on aorta and carotid artery from guinea pigs and on human subcutaneous arteries. Glibenclamide (10 μM), tolbutamide (1 mM), tolazamide (1 mM) and gliclazide (1 mM) all block contractions induced by U-46619, but not those induced by carbachol, on rat intrapulmonary bronchioles. However, prostanoid-induced contractions of guinea-pig trachea and main bronchi are not influenced by glibenclamide (10 μM). From these results it is concluded that the ability of sulfonylureas to block prostanoid-induced contractions is shared by all sulfonylureas tested, that this is not limited to vascular smooth muscle cells and that it shows a heterogeneity, that might be linked to interspecies differences. © 1997 Elsevier Science B.V.

Keywords: Sulfonylurea; Prostanoid; Thromboxane A_2; Prostaglandin $F_{2\alpha}$; Tolazamide; Tolbutamide; Gliclazide; Glibenclamide; Bronchiole; Artery

1. Introduction

Sulfonylureas are widely used as hypoglycemic drugs in the treatment of diabetes mellitus. By blocking ATP-regulated K^+ channels these drugs stimulate the pancreatic β-cells to release insulin (Davis and Granner, 1996).

Since the original observation published by Cocks et al. (1990), several papers reported that sulfonylureas are not only blockers of ATP-regulated K^+ channels, but that they also inhibit prostanoid-induced vasoconstriction (Nielsen-Kudsk and Thirstrup, 1991; Zhang et al., 1991; Zhang and Cook, 1994). Recently we reported that two sulfonylureas, glibenclamide and tolbutamide, exert an inhibitory influence on contractions of the rat aorta elicited by the prostanoids prostaglandin $F_{2\alpha}$, prostaglandin E_2 and the thromboxane A_2 mimetic U-46619, but not those elicited by norepinephrine, phenylephrine, serotonin, endothelin-1 or K^+ 120 mM. Since the contraction induced by activation of G-proteins with aluminium tetrafluoride anion (AlF_4^-) was also blocked by sulfonylureas, we speculated that the sulfonylureas might interfere in the signal transduction pathway used by prostanoids to induce smooth muscle cell contraction, possibly at the level of regulatory G-proteins (Delaey and Van de Voorde, 1995).

In the present study we investigated whether two other sulfonylureas, namely gliclazide and tolazamide, would have a similar specific inhibitory influence on prostanoid-induced contraction of the rat aorta. We also investigated whether the sulfonylureas would block prostanoid-induced contractions of various other blood vessels from different species, including humans. Finally we also investigated whether sulfonylureas can block prostanoid-induced contractions of another type of smooth muscle, namely in airway segments isolated from rats and guinea pigs.

2. Materials and methods

Experiments were performed on preparations dissected free of surrounding tissue and isolated from rats (male

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Wistar, 300 g), guinea pigs (500–600 g) and cattle (local slaughterhouse). Human arteries were dissected out of subcutaneous fat tissue obtained from women undergoing laparotomy for gynaecological reasons (approved by the Ethical Committee of the Medical Faculty of the University of Ghent).

2.1. Tension measurements

The greater preparations (trachea, main bronchi, carotid artery and thoracic aorta of the guinea pig; thoracic aorta of the rat) were studied using a classic organ bath set-up. The smaller preparations (rat intrapulmonary bronchioles and rat tail, femoral, renal interlobar arteries; bovine ciliary and retinal arteries; human subcutaneous arteries) were studied using an automated dual myograph (model 500 A, J.P. Trading, Aarhus, Denmark).

2.1.1. Classic organ bath experiments

Ring segments (2–4 mm length) were prepared and mounted in muscle chambers (20 ml) containing Krebs-Ringer bicarbonate solution at 37°C, through which a mixture of 95% O_2/5% CO_2 was bubbled. Rings were suspended under a tension of 0.5 g (rat aorta, guinea-pig carotid artery) or 1 g (guinea-pig aorta, trachea and main bronchi). Isometric force of contraction was measured with a force-displacement transducer (UC-2 cell Gould-Statham, Oxnard, CA, USA). The preparations were equilibrated under tension for 1 h before starting the measurements.

2.1.2. Automated myograph

After isolation, the preparations were transferred to the tissue chamber filled with 10 ml of Krebs-Ringer bicarbonate solution. Two stainless-steel wires (40 μm diameter) were guided through the lumen of segments with a length of 1.5–2 mm. One wire was fixed to a force-displacement transducer while the other was connected to a micrometer. After mounting, the preparations were allowed to equilibrate for 30 min in the Krebs-Ringer bicarbonate solution bubbled with 95% O_2/5% CO_2 and heated to 37°C. In experiments on blood vessels the arteries were then normalized as described by Mulvany and Halpern (1977). In brief, the passive wall tension-internal circumference characteristics were determined. On the basis of this relationship, the circumference was set to a normalized internal circumference (from which normalized diameter can be calculated) corresponding to 90% of the internal circumference the vessels would have under a passive transmural pressure of 100 mmHg, in order to obtain optimal conditions for active force development. After normalization, the preparations were allowed to equilibrate again for at least half an hour. In experiments on rat bronchioles, after mounting and 30 min of equilibration, the preparations were stretched to a wall tension of 0.8 mN/mm, found in a previous study to be optimal for developing active tension (Van de Voorde and Joos, 1996).

2.2. Drugs and statistics

The experiments with blood vessels were performed using a Krebs-Ringer bicarbonate solution of the following composition (in mmol/l): NaCl, 135; KCl, 5; $NaHCO_3$, 20; glucose, 10; $CaCl_2$, 2.5; $MgSO_4 \cdot 7H_2O$, 1.3; KH_2PO_4, 1.2; EDTA, 0.026. Experiments with airway segments were performed using a Krebs-Ringer bicarbonate solution with a slightly different composition: NaCl, 118; KCl, 4.6; $NaHCO_3$, 24.9; glucose, 5.5; $CaCl_2$, 2.5; $MgSO_4 \cdot 7H_2O$, 1.15; KH_2PO_4, 1.15. Krebs-Ringer bicarbonate solution with 120 mM K^+ was prepared by adequate equimolar replacement of NaCl with KCl.

U-44619 (9,11-dideoxy-11α,9α-epoxy-methanoprostaglandin $F_{2\alpha}$), carbamylcholine chloride (carbachol), norepinephrine bitartrate, 5-hydroxytryptamine creatinine sulfate complex (serotonin), glibenclamide and tolbutamide were obtained from Sigma (St. Louis, MO, USA). Tolazamide was obtained from Biomol (Plymouth Meeting, PA, USA), prostaglandin $F_{2\alpha}$ (dinoprostum trometamolum, Dinolytic) from Upjohn (Puurs, Belgium) and gliclazide was kindly provided by Institut de Reserches International Servier (IRIS, Courbevoie, France).

All concentrations are expressed as final molar concentrations in the organ bath. Concentration-response curves were made by cumulative additions of a small volume in the experimental chamber. All solutions were freshly prepared from appropriate stock solutions. Stock solutions were made in water except for glibenclamide and tolazamide, dissolved in dimethyl sulfoxide (DMSO), and tolbutamide, dissolved in ethanol. The final concentration of DMSO and ethanol was no more than 0.25%. Statistical significance was evaluated using Student's *t*-test for unpaired or paired observations. *n* indicates the number of preparations tested.

3. Results

3.1. Influence of gliclazide and tolazamide on prostanoid- and non-prostanoid-induced contractions of the rat aorta

In these series of experiments we compared the contractile effects of increasing concentrations of prostaglandin $F_{2\alpha}$, U-46619, norepinephrine, serotonin and K^+ 120 mM on rat aortic rings in the presence or absence of tolazamide (0.01, 0.1 and 1 mM) or gliclazide (0.01, 0.1 and 1 mM). Control and treated preparations were mounted in parallel in different organ chambers. The tissues were pre-incubated with the sulfonylureas for 10 min. Control preparations were incubated with the solvent. The results of these experiments are depicted in Figs. 1 and 2. They show that both sulfonylureas in a concentration of 1 mM have a pronounced inhibitory influence on the contractions induced by the prostanoids. On the other hand, the sulfony-

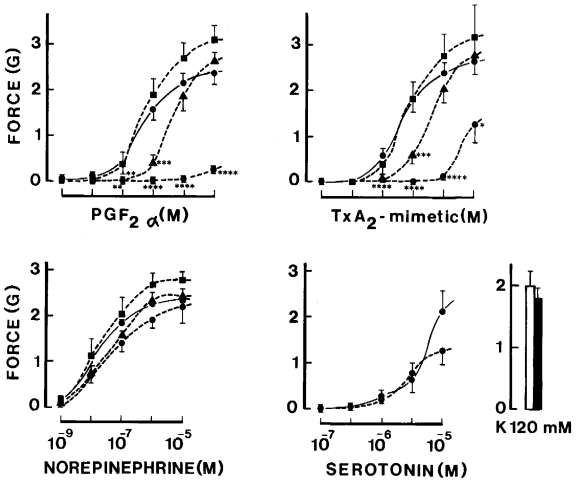

Fig. 1. Contraction (expressed as gram force) of rat aorta induced by increasing molar concentrations of prostaglandin $F_{2\alpha}$, U-46619, norepinephrine, serotonin and potassium 120 mM, in the absence (●————●, □) and presence of tolazamide 1 mM (●- - -●, ■), 0.1 mM (▲- - -▲) or 0.01 mM (■- - -■) ($n = 5$–6) (* $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$, **** $P < 0.001$).

lureas had much less influence on the contractions induced by the non-prostanoids.

3.2. Influence of glibenclamide on other rat arteries

In different series of experiments we investigated the influence of glibenclamide 10 μM on prostanoid-induced contractions in rat tail, femoral and renal interlobar arteries. Thirty minutes after normalizing these preparations (normalized diameters: tail artery = 562 ± 51 μm, $n = 5$; rat femoral artery = 422 ± 60 μm, $n = 5$; rat renal interlobar arteries = 305 ± 16 μm, $n = 6$–7), they were first maximally contracted three times using a mixture of K^+ 120 mM and norepinephrine 10 μM. Thereafter, control concentration-response curves (in the presence of the solvent of the sulfonylurea used further in the experiment) were constructed to prostaglandin $F_{2\alpha}$ or U-46619. After washing till baseline tension was again obtained, the preparations were exposed to glibenclamide (10 μM) for 10 min. Glibenclamide on itself did not elicit any effect. Then concentration-response curves to prostaglandin $F_{2\alpha}$ and the thromboxane A_2 mimetic were again constructed. As depicted in Fig. 3, the responses to prostaglandin $F_{2\alpha}$ and the thromboxane A_2 mimetic were much depressed in the presence of glibenclamide. Thereafter, the preparations were again washed and 30 min later the concentration-response curves to prostaglandin $F_{2\alpha}$ or the thromboxane A_2 mimetic were again constructed in the presence of the solvent. The responses were similar as in control conditions, illustrating the reversibility of the inhibitory influence of glibenclamide on the prostanoid-induced contractions.

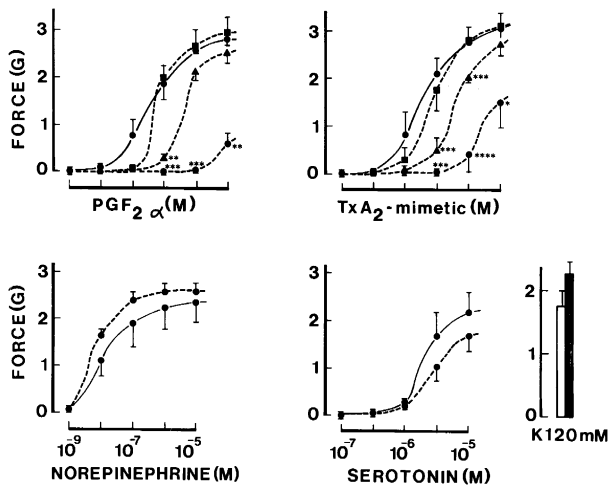

Fig. 2. Contraction (expressed as gram force) of rat aorta induced by increasing molar concentrations of prostaglandin $F_{2\alpha}$, U-46619, norepinephrine, serotonin and potassium 120 mM, in the absence (●————●, □) and presence of gliclazide 1 mM (●- - -●, ■), 0.1 mM (▲- - -▲) or 0.01 mM (■- - -■) ($n = 5$–6) (* $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$, **** $P < 0.001$).

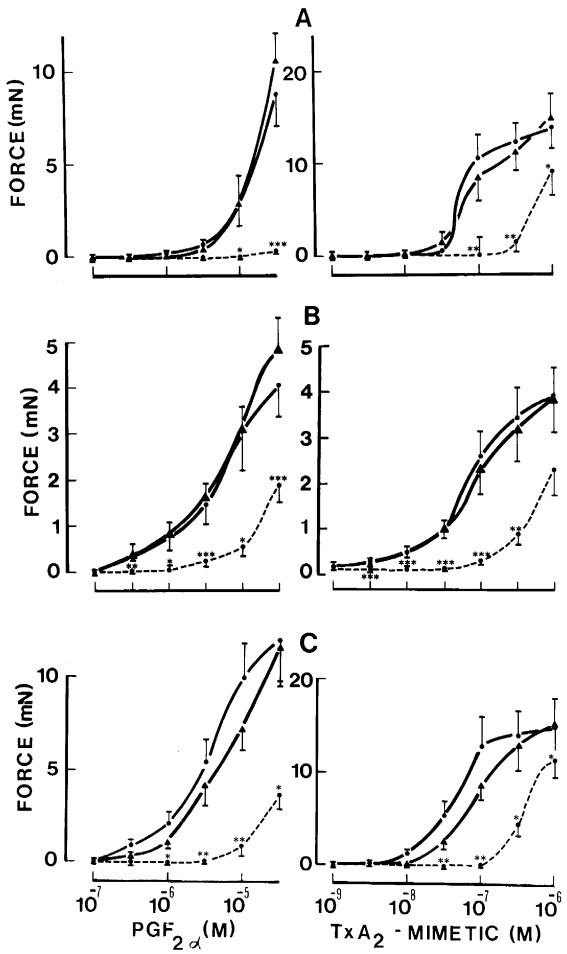

Fig. 3. Contraction (expressed as mN force) of rat tail artery ($n = 5$) (A), rat femoral artery ($n = 5$) (B) and rat interlobar artery ($n = 5$–7) (C) induced by increasing molar concentrations of prostaglandin $F_{2\alpha}$ or U-46619 in the absence (●————●), the presence (●- - -●) and after washout (▲————▲) of glibenclamide 10 μM ($n = 5$–7) (* $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$).

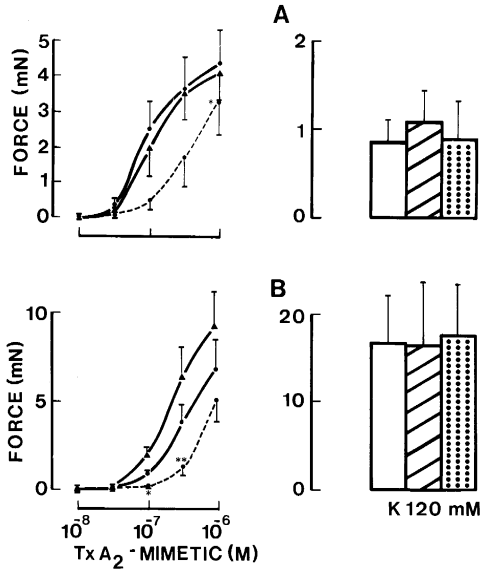

Fig. 4. Contraction (expressed as mN force) of bovine retinal artery ($n = 5$) (A) and bovine ciliary artery ($n = 6$) (B) induced by increasing molar concentrations of U-46619 and potassium 120 mM, in the absence (●————●, open column), presence (●- - -●, hatched column) and after washout (▲————▲, stippled column) of glibenclamide 10 μM. (* $P < 0{,}05$, ** $P < 0{,}02$).

3.3. Bovine retinal and ciliary arteries

Retinal and ciliary arteries were isolated from bovine eyes and mounted in the myograph. Thirty minutes after normalization (normalized diameters: retinal artery = 203 ± 17 μm, $n = 6$; ciliary artery = 245 ± 34 μm, $n = 5$) these preparations were three times contracted with K^+ 120 mM. Maximal contractile force was assessed using a mixture of K^+ 120 mM, serotonin 10 μM and prostaglandin $F_{2\alpha}$ 30 μM. Thereafter retinal and ciliary arteries were exposed to increasing concentrations of the thromboxane A_2 mimetic and K^+ 120 mM in the presence of 0.25% DMSO. These responses were reassessed in the presence of glibenclamide (pre-incubation for 10 min). The response to the thromboxane A_2 mimetic was less pronounced while that to K^+ 120 mM was not diminished (Fig. 4). Thirty minutes after washing the preparations, the response to the thromboxane A_2 mimetic was similar or even somewhat more pronounced than in control conditions.

3.4. Guinea-pig thoracic aorta and carotid artery

In these experiments we investigated the contractile effects of increasing concentrations of prostaglandin $F_{2\alpha}$ and U-46619 on control guinea-pig aortic rings and in parallel on rings incubated for 10 min with glibenclamide (10 μM). Glibenclamide does not significantly affect the prostanoid-induced contractions on these preparations. The results of the experiments on the guinea-pig aorta are depicted in Fig. 5.

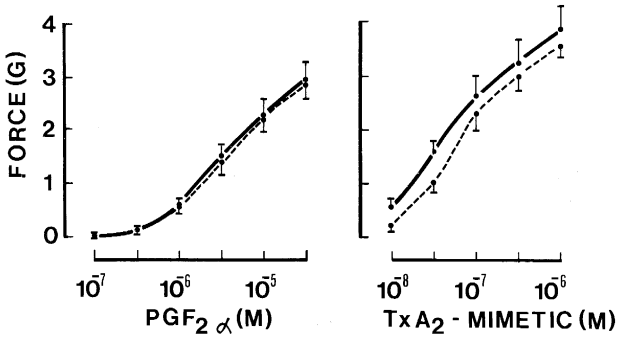

Fig. 5. Contraction (expressed as gram force) of guinea-pig thoracic aorta induced by increasing molar concentrations of prostaglandin $F_{2\alpha}$ and U-46619, in the absence (●————●) and presence (●- - -●) of glibenclamide 10 μM ($n = 6$–9).

3.5. Human subcutaneous arteries

Thirty minutes after normalization (normalized diameter = 156 ± 10 μm, $n = 6$) these preparations were contracted three times with a mixture of K^+ 120 mM and norepinephrine 10 μM. Then a control concentration-response curve was made with U-46619 in the presence of 0.25% DMSO. Thereafter the preparations were washed and exposed to glibenclamide 10 μM for 10 min. Glibenclamide on itself did not elicit any effect. Then the concentration-response curve with the thromboxane A_2 mimetic was repeated in the presence of glibenclamide. The response was not significantly different from the control response. After 30 min of washing, the response to the thromboxane A_2 mimetic was reassessed. The results are depicted in Fig. 6.

3.6. Bronchial smooth muscle cells

3.6.1. Rat bronchioles

In these experiments we investigated the influence of glibenclamide (10 μM), tolbutamide (1 mM), tolazamide (1 mM) and gliclazide (1 mM) on contractions induced by increasing concentrations of U-46619 and of carbachol on rat bronchioles (diameter 250–500 μm). Thirty minutes

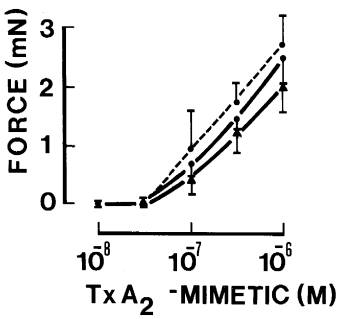

Fig. 6. Contraction (expressed as mN force) of human subcutaneous arteries induced by increasing molar concentrations of U-46619 in the absence (●————●), presence (●- - -●) and after washout (▲————▲) of glibenclamide 10 μM ($n = 6$).

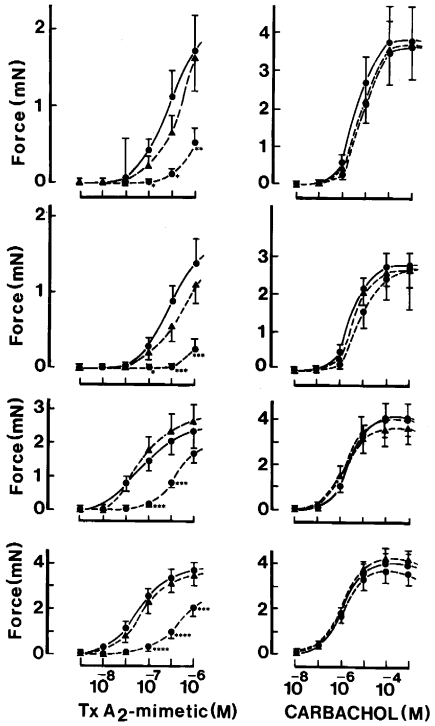

Fig. 7. Contraction (expressed as mN force) of rat bronchioles induced by increasing molar concentrations of U-46619 and carbachol in the absence (● ——— ●), presence (●- - -●) and after washout (▲- - -▲) of (in descending order) glibenclamide 10 μM ($n = 6$), tolbutamide 1 mM ($n = 6$), tolazamide 1 mM ($n = 6–8$) or gliclazide 1 mM ($n = 6–7$) (* $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$, **** $P < 0.001$).

after stretching the preparations to the optimal wall tension, the preparations were twice contracted with K^+ 120 mM and carbachol 0.1 mM, after which control concentration-response curves were constructed with the thromboxane A_2 mimetic and carbachol (in the presence of the solvent of the sulfonylurea tested further in the experiment). Thereafter the preparations were exposed to one of the sulfonylureas for at least 10 min and the curves were again constructed in the presence of one of the sulfonylureas. Finally, after washing the preparations for 30 min, the curves were again constructed. The results of these experiments are depicted in Fig. 7. They illustrate the profound and reversible inhibitory influence of all tested sulfonylureas on the thromboxane A_2 mimetic-induced contraction, without influencing carbachol-induced contractions.

3.6.2. Guinea-pig trachea and main bronchi

One hour after mounting, the preparations were exposed to K^+ 120 mM and carbachol 100 μM, eliciting maximal contraction. Then control concentration-response curves were made with the thromboxane A_2 mimetic or prostaglandin $F_{2\alpha}$ in the presence of 0.25% DMSO. After washing, the tissues were exposed to glibenclamide 10 μM for 10 min and the concentration-response curve was again constructed. No significant inhibitory influence of glibenclamide was found on the prostanoid-induced contraction.

4. Discussion

In recent years evidence has been provided that sulfonylureas are not only blockers of ATP-dependent K^+ channels, but that they also have an inhibitory influence on prostanoid-induced vasoconstriction. The relationship between the ability of sulfonylureas to inhibit prostanoid-induced contractions and to antagonize ATP-dependent K^+ channels is not evident. Indeed, blockers of K^+ channels are not expected to induce relaxation of smooth muscle cells, but rather contraction.

Cocks et al. first reported in 1990 that glibenclamide behaves as a competitive antagonist of U-46619 in isolated dog coronary arteries (Cocks et al., 1990). Nielsen-Kudsk and Thirstrup (1991) found that five different sulfonylureas relax prostaglandin $F_{2\alpha}$-precontracted isolated rabbit coronary arteries. Since the effectiveness of the sulfonylureas as vascular smooth muscle relaxants did not correlate with their antagonistic action against vasorelaxation responses to cromakalim, these authors suggested that another mechanism than interaction with ATP-sensitive K^+ channels underlies sulfonylurea-induced vasorelaxation. In 1991 Zhang et al. reported that glibenclamide causes relaxation of prostaglandin $F_{2\alpha}$-precontracted rat aorta and canine femoral, mesenteric, renal, coronary, basilar and middle cerebral arteries (Zhang et al., 1991). Later they found that glibenclamide, glipizide and tolbutamide significantly inhibit the contractions on rat aorta elicited by not only prostaglandin $F_{2\alpha}$, but also by prostaglandins E_2 and D_2 (Zhang and Cook, 1994).

Recently we reported that the sulfonylureas glibenclamide and tolbutamide block, in a specific way, contractions of rat aorta induced by prostaglandin $F_{2\alpha}$, prostaglandin E_2 and U-46619. This inhibition is independent of the presence of endothelium. These sulfonylureas also block AlF_4^--induced contractions (activating G-proteins) but not contractions elicited by other agonists that also elicit contraction through activation of phospholipase C (e.g., phenylephrine). This thus suggests that the site of interference of sulfonylureas in the signal transduction process of the prostanoids might be situated at the level of the regulatory G-proteins (Delaey and Van de Voorde, 1995).

The present paper provides evidence that prostanoid-induced contractions of the rat aorta are not only blocked by glibenclamide and tolbutamide, but also by two other sulfonylureas, namely gliclazide and tolazamide. This inhibitory influence is reversible and specific since contractions elicited with serotonin, norepinephrine and high potassium are not influenced.

The ability of sulfonylureas to block prostanoid-induced contractions is not limited to the rat aorta. It is observed on

all the arteries studied from the rat: carotid artery, tail artery, femoral artery and renal interlobar arteries. The present study also provides evidence that sulfonylureas block prostanoid-induced contractions in bovine arteries since contractions induced by U-46619 (and not by K^+ 120 mM) on bovine retinal and ciliary arteries are significantly blocked by glibenclamide.

The ability of sulfonylureas to block prostanoid-induced contractions seems not to be limited to vascular tissue. All four sulfonylureas used in the present study greatly reduce, in a reversible and specific manner, contractions of rat small bronchioles induced by U-46619. This thus substantially extends the importance of previous studies which were all performed on vascular tissue. Since prostanoids are considered to be important mediators of bronchial hyperreactivity (Chung and Barnes, 1992) and since drugs can relatively selectively be administered into the bronchial tree by inhalation, these findings might be of pharmacological interest.

However, the ability of sulfonylureas to block prostanoid-induced contractions cannot be generalized. On guinea-pig thoracic aorta and on human subcutaneous small arteries, prostanoid-induced contractions are not blocked by glibenclamide, the most potent of the sulfonylureas used in this study. The reason for the heterogeneous influence of sulfonylureas on prostanoid-induced contractions is unclear. It might be related to interspecies differences. An argument in favor of this is the fact that prostanoid-induced contractions are not blocked in both aorta and airway segments isolated from the guinea pig. In this respect it is interesting to mention that interspecies differences in smooth muscle receptors activated by prostanoids have been reported. Ogletree and Allen (1992) concluded from a study performed on airway and vascular smooth muscle from rat and guinea pig that the TP (thromboxane A_2/prostaglandin endoperoxide) prostanoid receptors in smooth muscles from guinea pigs are different from those in rats but, within each species, quite similar. While the thromboxane A_2 mimetic is a selective agonist of the TP prostanoid receptor subtype, it is known that prostaglandin $F_{2\alpha}$ has also an appreciable agonist activity at the TP prostanoid receptor subtype (Coleman et al., 1994). Interesting with respect to interspecies differences in TP prostanoid receptors is the fact that platelet TP receptors of guinea pig most closely resemble the human, whereas the dog, rabbit and rat receptors differ considerably from the human and each other (Halushka et al., 1989). Whether this can be related to the fact that sulfonylureas inhibit prostanoid-induced contractions in preparations from dogs (Cocks et al., 1990), rabbits (Nielsen-Kudsk and Thirstrup, 1991) and rats (Zhang and Cook, 1994; Delaey and Van de Voorde, 1995, present paper), but not from guinea pigs or from humans (present paper) is an attractive hypothesis that remains to be proven. However, if this hypothesis proves to be correct, then the sulfonylureas might be useful tools to discriminate between TP prostanoid receptor subtypes.

Acknowledgements

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