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European Journal of Pharmacology 426 (2001) 89–94

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# Differential effects of prostacyclin and iloprost in the isolated carotid artery of the guinea-pig

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Received 19 April 2001; received in revised form 5 July 2001; accepted 10 July 2001

**Abstract**

The effects on membrane potential of prostacyclin and iloprost were compared in smooth muscle cells of the guinea pig carotid artery. Both prostacyclin and iloprost induced hyperpolarization of the smooth muscle cells. In the presence of (3*R*)-3-(4-fluorophenylsulfonamido)-1,2,3,4-tetrahydro-9-carbazolepropanoic acid (Bay U3405), an antagonist of TP receptors, the response to iloprost was unaffected while that to prostacyclin was increased. Iloprost-induced hyperpolarizations were abolished by glibenclamide while those to prostacyclin were either not affected, or converted to either depolarization or to rhythmic electrical activity. The latter effects of prostacyclin were abolished by Bay U3405. After removal of the endothelium, iloprost and prostacyclin produced hyperpolarizations similar to those observed in control blood vessels. However, in the presence of glibenclamide, prostacyclin produced only depolarizations inhibited by Bay U3405. These results suggest that iloprost activates IP receptors and $K_{ATP}$ channels in smooth muscle. In contrast, prostacyclin produces additional endothelium-dependent and -independent effects via activation of TP receptors. 

*Keywords:* Prostacyclin; Iloprost; Hyperpolarization; Membrane potential; $K^+$ channel; Smooth muscle cell, vascular

## 1. Introduction

Prostacyclin, the principal metabolite of arachidonic acid produced by endothelial cyclooxygenase (Moncada et al., 1976, 1977), causes vasodilatation in most blood vessels (Kadowitz et al., 1978). This involves the stimulation of specific cell-surface receptors (IP receptors) that are associated with the activation of adenylate cyclase (Gryglewski et al., 1991; Wise and Jones, 1996), and in some instances with the hyperpolarization of the vascular smooth muscle cells (Jackson et al., 1993; Parkington et al., 1995). However, at higher concentrations, prostacyclin can evoke biphasic responses or contractions in some vascular tissues including human arteries (Pomerantz et al., 1978; Davis et al., 1980; Borda et al., 1983; Kaapa et al., 1991; Williams et al., 1994). These contractions are linked either to the direct activation of TP receptors (Zhao et al., 1996) or to the release of endothelium-derived contracting factor(s) (Adeagbo and Malik, 1990; Rapoport and Williams, 1996).

The purpose of the present study was to compare the changes in membrane potential produced by prostacyclin and its stable analogue iloprost, in smooth muscle cells of the guinea-pig carotid artery.

## 2. Material and methods

### 2.1. Electrophysiology

Male Hartley guinea-pigs (300–400 g, Charles River, France) were anaesthetised with pentobarbitone (250 mg/kg, i.p.) and the carotid arteries were dissected, cleaned of adherent connective tissue and pinned down to the bottom of an organ chamber (1 ml). They were continuously superfused with modified Krebs-Ringer bicarbonate solution (37 °C, aerated with a 95% $O_2$, 5% $CO_2$ gas

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0014-2999/01/$ - see front matter 
PII: S0014-2999(01)01203-1

mixture; pH: 7.4) of the following composition (mM): NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $KH_2PO_4$ 1.2, $NaHCO_3$ 25, calcium disodium EDTA 0.026 and glucose 11.1.

In most experiments, care was taken to preserve the integrity of the endothelium. In some experiments, the endothelium was removed with a rapid infusion of saponin (1 mg/ml) into the lumen of the blood vessel (Corriu et al., 1996). Transmembrane potentials were recorded with glass microelectrodes filled with KCl (3 M), with a tip resistance of 30 to 90 MΩ. The potential recorded was amplified by means of a recording preamplifier (WPI intra767, New Haven, CT, USA) with capacitance-neutralization. Impalements were not accepted as valid unless they were signaled by a sudden change in voltage, and were maintained for at least 3 min; at that point the membrane potential had stabilized. The impalements were performed from the adventitial side. In order to prevent the release of endogenous endothelial factors, indomethacin ($5 \times 10^{-6}$ M) and $N^G$-nitro-L-arginine (L-NA, $10^{-4}$ M) were present throughout the experiments.

### 2.2. Drugs

Indomethacin; $N^{\omega}$-L-nitro-arginine (L-NA); prostacyclin, prostaglandin $E_2$, Prostaglandin $F_{2\alpha}$, 6-keto-Prostaglandin $F_{1\alpha}$, 9,11-dideoxy-9α,11α-methanoepoxyprostaglandin $F_{2\alpha}$ (U46619, Sigma, La Verpillère, France); charybdotoxin, apamin (Latoxan, Rosans, France); glibenclamide (Boehringer, Manheim, Germany); iloprost (Schering, Berlin, Germany); (3*R*)-3-(4-fluorophenylsulfonamido)-1,2,3,4-tetrahydro-9-carbazolepropanoic acid (Bay U3405, Servier, Suresnes, France). Prostacyclin was dissolved in Tris(hydroxymethyl)-aminomethan (50 mM, pH = 9.4). Stock solution of glibenclamide and 6-keto-Prostaglandin $F_{1\alpha}$ were prepared in dimethylsulfoxide ($10^{-3}$ M), indomethacin ($5 \times 10^{-4}$ M) in $NaHCO_3$ (50%), prostaglandin $E_2$ and U 46619 ($10^{-3}$ M) in ethanol (70%). Other drugs were dissolved in distilled water.

### 2.3. Statistics

Data are shown as mean ± S.E.M.; *n* indicates the number of cells in which membrane potential was recorded. Statistical analysis was performed with Student's *t*-test for unpaired observations. Differences were considered to be statistically significant when *P* was less than 0.05.

## 3. Results

### 3.1. Arteries with endothelium

In the presence of endothelium, the membrane potential of the guinea pig carotid artery smooth muscle cells averaged $-55.8 \pm 0.7$ mV ($n = 72$). Prostacyclin ($10^{-9}$–$10^{-5}$ M) induced a concentration-dependent hyperpolarization and at the highest concentration tested induced a biphasic hyperpolarization. A first transient hyperpolarization ($-7.6 \pm 1.1$ mV, $n = 10$) was followed by a sustained hyperpolarization ($-12.3 \pm 2.5$ mV, $n = 4$). Iloprost ($10^{-9}$–$10^{-6}$ M) produced concentration-dependent sustained hyperpolarizations that were significantly larger than those produced by prostacyclin (Figs. 1 and 2).

The membrane potential of smooth muscle cells was not influenced by the presence of the antagonist of TP receptors Bay U3405 ($10^{-6}$ M, $-55.2 \pm 1.0$ mV, $n = 47$). In the presence of Bay U3405, the concentration–response curve to prostacyclin was shifted to the left and the amplitude of the hyperpolarization was enhanced (Fig. 2). The TP receptor antagonist did not significantly affect the hyperpolarization induced by iloprost (Fig. 2). In the

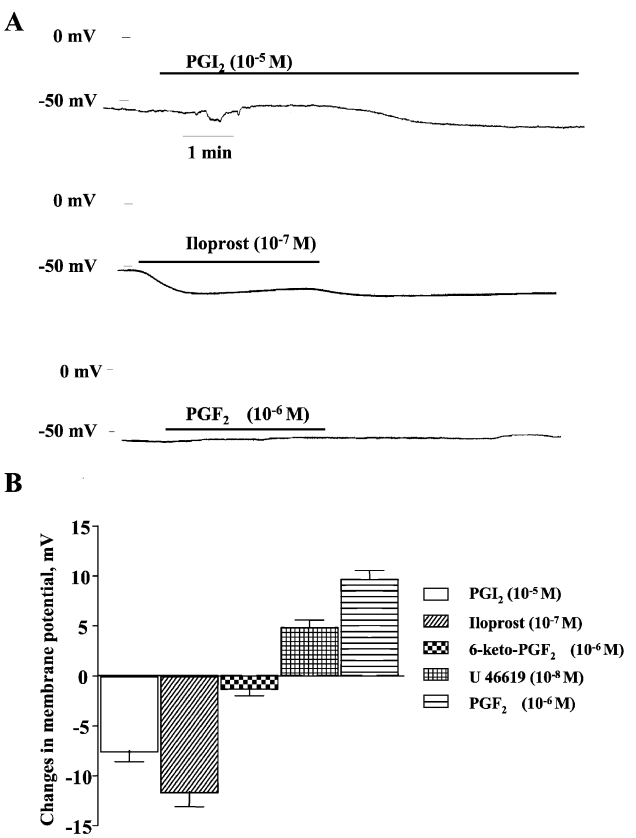



Fig. 1. Effects of some prostaglandins and their analogues on the membrane potential of the smooth muscle cells of guinea-pig carotid artery with endothelium [in the presence of indomethacin ($5 \times 10^{-6}$ M) plus L-nitro-arginine ($10^{-4}$ M)]. (A) Original recordings showing changes in the membrane potential to prostacyclin ($PGI_2$, $10^{-5}$ M), iloprost ($10^{-7}$ M) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, $10^{-6}$ M). (B) Summary graphs showing the changes in membrane potential produced by prostacyclin ($PGI_2$, $10^{-5}$ M, transient hyperpolarization), iloprost ($10^{-7}$ M), 6-keto-prostaglandin $F_{2\alpha}$ (6-keto-$PGF_{2\alpha}$, $10^{-6}$ M), U 46619 ($10^{-8}$ M) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, $10^{-6}$ M). Data are shown as means ± S.E.M., ($n = 3$–10).

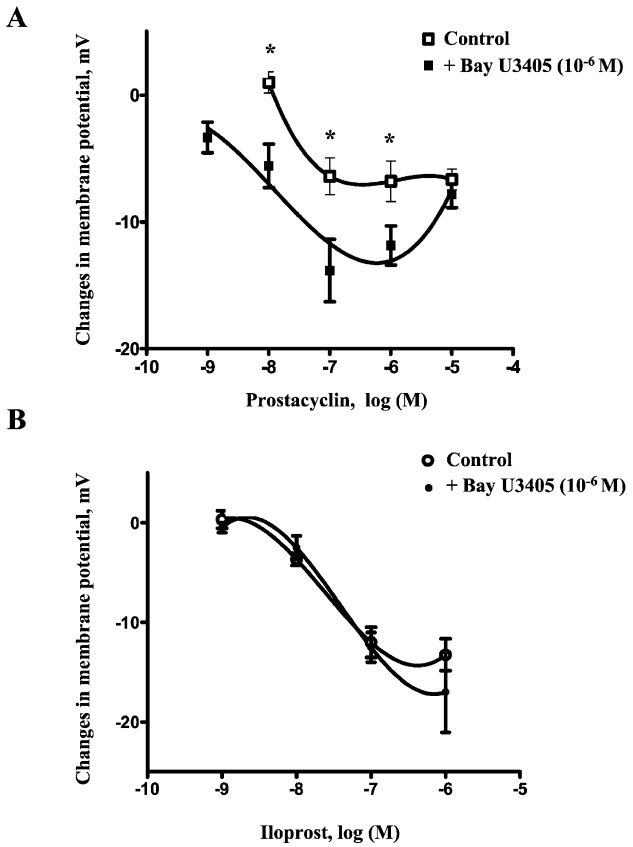



Fig. 2. Effect of Bay U3405 ($10^{-6}$ M) on the changes in membrane potential, produced by prostacyclin and iloprost in smooth muscle cells of the guinea-pig carotid artery with endothelium [in the presence of indomethacin ($5\times10^{-6}$ M) plus L-nitro-arginine ($10^{-4}$ M)]. (A) Concentration–response curves to prostacyclin (transient hyperpolarization). Bay U3405 ($10^{-6}$ M) produced a significant leftward shift of the concentration–response curve and an increase in the maximal hyperpolarization. (B) Concentration–response curves to iloprost. Bay U3405 ($10^{-6}$ M) did not produce significant changes in the response. Data are shown as means ± S.E.M. ($n = 3$–10). The asterisk indicates a statistically significant difference.

presence of Bay U3405, the effects of prostacyclin were no longer significantly different than the effects of iloprost.

Prostaglandin $E_2$ ($10^{-6}$ M) and two agonists at TP receptors, U46619 ($10^{-8}$ M) and prostaglandin $F_{2\alpha}$ ($10^{-6}$ M), depolarized the smooth muscle cells membrane (Fig. 1). The effects of U46619 and prostaglandin $F_{2\alpha}$ were abolished in the presence of Bay U3405 ($0.0 \pm 0.7$ and $0.3 \pm 0.8$ mV, $n = 3$ for U46619 and prostaglandin $F_{2\alpha}$, respectively). The metabolite of prostacyclin, 6-keto-prostaglandin $F_{1\alpha}$ ($10^{-5}$ M), did not significantly influence the membrane potential ($-1.3 \pm 0.7$ mV, $n = 3$; Fig. 1).

Glibenclamide ($10^{-6}$ M) itself did not influence the membrane potential of the smooth muscle cells ($-53.3 \pm 1.2$ mV, $n = 38$). However, in the presence of glibenclamide, prostacyclin ($10^{-5}$ M) depolarized 39% of the cells ($+7.4 \pm 1.4$ mV, $n = 9$; Fig. 3), hyperpolarized 30% of the cells studied ($-11.7 \pm 3.5$ mV, $n = 7$; Fig. 3), or induced spontaneous electrical activity in the remaining 30% of the cells ($n = 7$; Fig. 3). By contrast, the hyperpolarization induced by iloprost ($10^{-7}$ M) was fully and consistently blocked by glibenclamide ($+0.5 \pm 1.0$ mV, $n = 4$; Fig. 3).

In the presence of glibenclamide, and after the addition of the combination of charybdotoxin ($10^{-7}$ M) plus apamin ($5 \times 10^{-7}$ M), prostacyclin depolarized all the cells studied (Fig. 4). In the presence of glibenclamide and after the addition of Bay U3405 ($10^{-6}$ M), prostacyclin ($10^{-5}$ M) no longer influenced the membrane potential (Fig. 4).

### 3.2. Arteries without endothelium

In the absence of the endothelial cells, the membrane potential of the smooth muscle was significantly less than

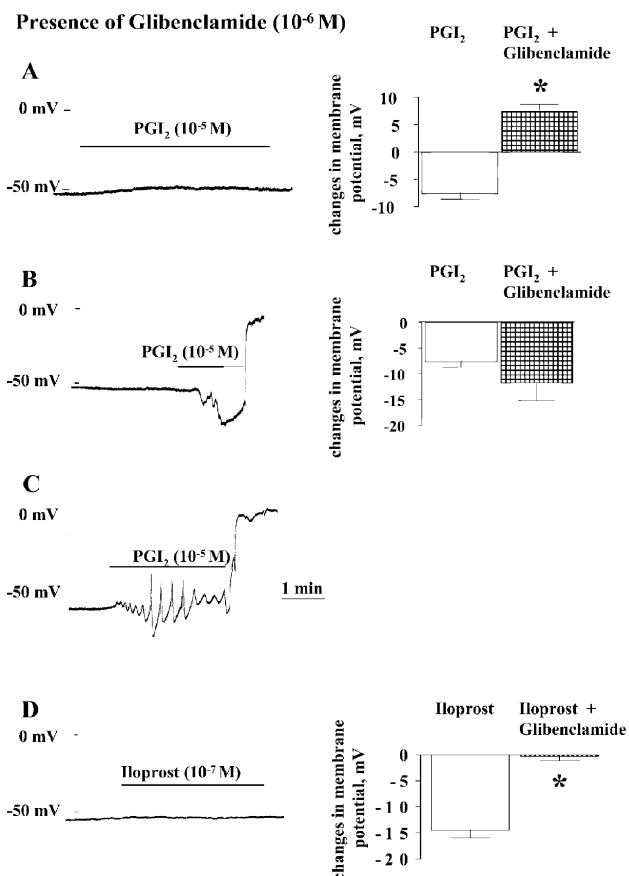
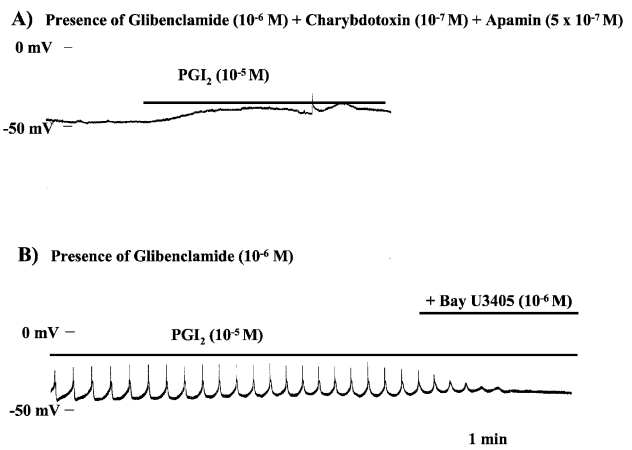



Fig. 3. Effects of glibenclamide ($10^{-6}$ M) on the hyperpolarizations induced by prostacyclin ($PGI_2$: $10^{-5}$ M) and iloprost ($10^{-7}$ M) in smooth muscle cells of the guinea-pig carotid artery with endothelium (presence of indomethacin: $5\times10^{-6}$ M plus L-nitro-arginine: $10^{-4}$ M). Left panels: original recordings; (A) prostacyclin ($10^{-5}$ M) induced a depolarization in 9 out of 23 cells. (B) Prostacyclin ($10^{-5}$ M) induced a hyperpolarization in 7 out of 23 cells. (C) Prostacyclin ($10^{-5}$ M) induced spike-like rhythmic activity in 7 out of 23 cells. (D) Iloprost ($10^{-7}$ M). Right panels: summary graphs; data are shown as means ± S.E.M. ($n$ = 4–9). The asterisk indicates a statistically significant difference between the changes in membrane potential observed under control conditions and in the presence of glibenclamide ($10^{-6}$ M).

in their presence and averaged $-51.9 \pm 1.1$ mV ($n = 29$). Iloprost ($10^{-7}$ M) produced a sustained hyperpolarization ($-16.6 \pm 1.9$ mV, $n = 6$) that was not significantly different from that observed in arteries with endothelium (Fig. 5). Similarly, the effects of prostacyclin ($10^{-5}$ M) were not affected by the removal of the endothelial cells. Thus, a hyperpolarization was observed that was biphasic with an initial transient phase ($-8.6 \pm 1.5$ mV, $n = 8$) followed by a sustained second phase ($-11.3 \pm 2.4$ mV, $n = 4$). In the presence of Bay U3405 ($10^{-6}$ M), a statistically significant increase of the maximal hyperpolarization to prostacyclin was observed, especially during the sustained second phase ($-11.3 \pm 2.4$ and $-18.0 \pm 1.8$ mV, $n = 4$, in the absence and presence of Bay U3405, respectively; Fig. 5). In the presence of glibenclamide ($10^{-6}$ M), prostacyclin ($10^{-5}$ M) consistently produced a depolarization



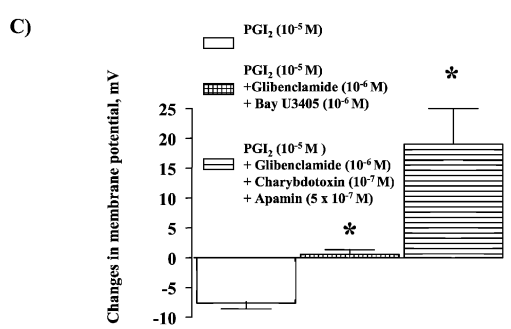




Fig. 4. Glibenclamide ($10^{-6}$ M) and the changes in membrane potential induced by prostacyclin ($PGI_2$: $10^{-5}$ M) in the smooth muscle cells of the guinea-pig carotid artery with endothelium [in the presence of indomethacin ($5 \times 10^{-6}$ M) plus L-nitro-arginine ($10^{-4}$ M)]. (A) Original recording showing the effect of the association of charybdotoxin ($10^{-7}$ M) plus apamin ($5 \times 10^{-7}$ M). B) Original recording showing the effect of Bay U3405 ($10^{-6}$ M). (C) Summary graphs. Data are shown as means ± S.E.M. ($n = 4$–9). The asterisk indicates a statistically significant difference between the changes in membrane potential observed under control condition and after treatment.

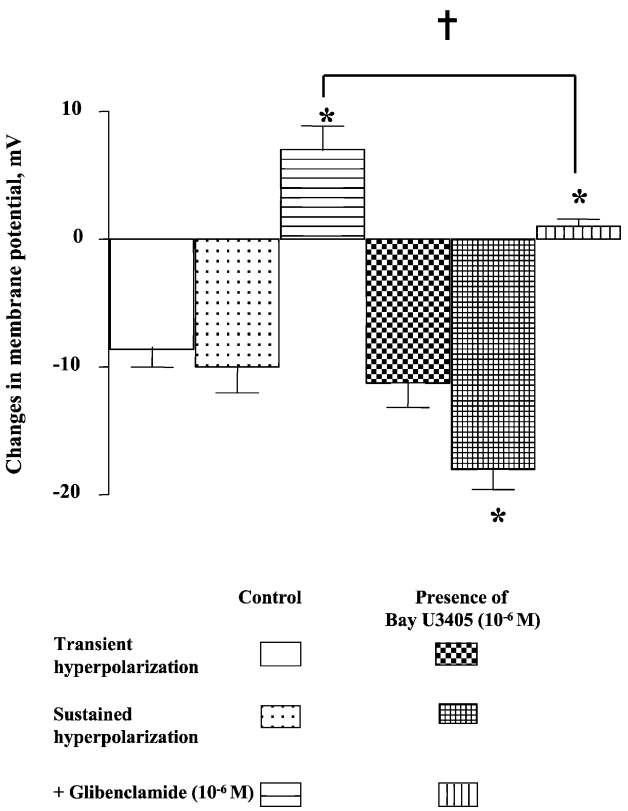



Fig. 5. Prostacyclin ($PGI_2$, $10^{-5}$ M)-induced changes in membrane potential of the smooth muscle cells of guinea-pig carotid arteries without endothelium [in the presence of indomethacin ($5 \times 10^{-6}$ M) plus L-nitro-arginine ($10^{-4}$ M)]. Effects of glibenclamide ($10^{-6}$ M), Bay U3405 ($10^{-6}$ M) and glibenclamide plus Bay U3405. Data are shown as means ± S.E.M. ($n = 3$–8). The asterisk indicates a statistically significant difference between the sustained hyperpolarization induced by prostacyclin in control conditions and the changes in membrane potential observed in the presence of drugs. The dagger indicates a statistically significant difference between the effect of prostacyclin in the presence of glibenclamide only and that observed in the presence of glibenclamide plus Bay U3405.

($6.6 \pm 1.8$ mV, $n = 7$) that was abolished by Bay U3405 ($10^{-6}$ M; $1.0 \pm 0.7$ mV, $n = 3$; Fig. 5).

## 4. Discussion

In the present study, prostacyclin and its stable analogue iloprost induced a hyperpolarization of the guinea-pig vascular smooth muscle cells, confirming earlier results obtained in various species (Siegel et al., 1981; Parkington et al., 1993, 1995; Murphy and Brayden 1995; Corriu et al., 1996). These hyperpolarizations were observed in vessels treated with inhibitors of nitric oxide synthase and cyclooxygenase and in vessels with or without endothelium, indicating a direct activation of a smooth muscle receptor. Iloprost has a high affinity not only for IP receptors but also for $EP_1$ and $EP_3$ receptors (Narumiya et

al., 1999). However, the receptor involved in the hyperpolarization induced by prostacyclin and iloprost is most likely to be the IP receptor since prostaglandin $E_2$, an agonist of the $EP_1$ and $EP_3$ receptors (Narumiya et al. 1999), depolarized the smooth muscle cells of the guinea-pig carotid artery. Under the present experimental conditions, the hyperpolarizations produced by iloprost were similar in vessels with and without endothelium and were fully blocked by glibenclamide, indicating that the prostacyclin analogue activates exclusively IP receptors and ATP-sensitive potassium channels on smooth muscle.

The hyperpolarization produced by prostacyclin (or its various analogues) is usually attributed to the opening of ATP-sensitive $K^+$ channels since they are inhibited by sulfonylureas such as glibenclamide (Siegel et al., 1981; Jackson et al., 1993; Parkington et al., 1993, 1995; Murphy and Brayden 1995; Corriu et al., 1996). However, in the carotid artery of the guinea-pig, prostacyclin shows an additional effect when compared to iloprost. In blood vessels without endothelium, the hyperpolarization induced by prostacyclin was enhanced by Bay U3405, an antagonist of TP receptors, suggesting that prostacyclin simultaneously activates IP and TP receptors on these smooth muscles and that these interactions produce opposite effects on the membrane potential. This is further confirmed by the observations that in the presence of glibenclamide, prostacyclin produces a depolarization blocked by Bay U3405, and that the TP receptor agonist prostaglandin $F_{2\alpha}$ and the thromboxane $A_2$ analogue U 46619 also produce depolarizations sensitive to Bay U3405. Whether or not the TP receptors are activated directly by prostacyclin or by a metabolite is uncertain. However, 6-keto-prostaglandin $F_{1\alpha}$, the principal metabolite of prostacyclin (Moncada and Vane 1979), does not appear to activate TP receptors.

In blood vessels with endothelium, the concentration–response curve to prostacyclin was shifted to the left by Bay U3405, confirming that prostacyclin activates simultaneously IP and TP receptors. In the presence of glibenclamide, the results obtained in 30% of the arteries studied were consistent with what was observed in blood vessels without endothelium. Thus, prostacyclin produced a depolarization sensitive to Bay U3405. However, in the other blood vessels and in contrast to iloprost, glibenclamide either did not affect the hyperpolarization produced by prostacyclin or unmasked spike-like repetitive electrical activity. These endothelium-dependent effects of prostacyclin, unmasked by glibenclamide (hyperpolarization or spike-like activity), were inhibited by charybdotoxin plus apamin. Indeed, in the presence of these two $K^+$ channel blockers, the effects of prostacyclin were similar to those observed in carotid arteries without endothelium. Furthermore, in the presence of the TP receptor antagonist, all the effects of prostacyclin unmasked by glibenclamide were fully inhibited.

Sulfonyureas, such as glibenclamide and to a lesser extent tolbutamide, inhibit thromboxane receptors at high concentrations (Cocks et al., 1990; Zhang et al., 1991). This could explain the complex changes observed in the presence of glibenclamide and prostacyclin as both substances may interact with the TP receptors. However, the addition of Bay U3405 produced clear-cut inhibition of the responses, suggesting that this unspecific action of glibenclamide is unlikely to explain the effects of prostacyclin. These results in fact suggest that prostacyclin (or a metabolite different from 6-keto-prostaglandin $F_{1\alpha}$) activates calcium-sensitive $K^+$ channels. Whether or not this endothelial effect involves the release of a factor or the transmission of electrical changes to the smooth muscle via myo-endothelial gap junctions remain to be determined. However, if a factor were released it could not be nitric oxide (NO) or a cyclooxygenase product as experiments were performed in the presence of inhibitors of NO-synthase and cyclooxygenase.

The results of the present study collectively suggest that in the guinea-pig carotid artery, iloprost activates IP receptor on the smooth muscle cells and produces hyperpolarization by opening ATP-sensitive $K^+$ channels. In contrast, prostacyclin (or a metabolite different from 6-keto-prostaglandin $F_{1\alpha}$) produces additional endothelium-dependent and -independent effects that are prevented by a TP receptor antagonist.

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