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Effects of glibenclamide on systemic and splanchnic haemodynamics in conscious rats

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1 The effects of the sulphonylurea, glibenclamide (20 mg kg^{-1}, i.v.), at a dose that blocks vascular potassium channels, on systemic and splanchnic haemodynamics (radioactive microspheres) were studied in conscious rats.

2 Glibenclamide significantly decreased cardiac index and hepatic artery blood flow while it significantly increased vascular resistance in systemic, portal and hepatic arterial territories.

3 In rats with suppressed cardiovascular reflexes, glibenclamide induced vasoconstriction in systemic, portal and hepatic arterial territories.

4 Intracerebroventricular administration of glibenclamide did not alter systemic or regional vascular tone.

5 Glibenclamide blunted the vasodilator effect of the potassium channel opener, diazoxide but not that of the L-type calcium channel blocker, nicardipine.

6 Another sulphonylurea, glipizide (20 mg kg^{-1}, i.v.), induced significant systemic and splanchnic vasoconstriction.

7 Thus, the glibenclamide-induced blockade of vascular potassium channels caused a vasoconstriction in the systemic and splanchnic vascular beds. In these territories, therefore, the opening of glibenclamide-sensitive potassium channels might be responsible for a basal vasodilator tone.

Keywords: Glibenclamide; glipizide; sulphonylurea; K^+-channels; vascular tone

Introduction

While the vasodilator effect of potassium channel openers, such as cromakalim or diazoxide has been clearly established (Quast & Cook, 1989; Weston & Edwards, 1991), the vascular effect of the sulphonylureas, such as glibenclamide, which are potassium channel blockers, is unclear. On one hand, since it has been shown that glibenclamide inhibits the vasodilator effect of potassium channel openers (Wilson *et al.*, 1988; Buckingham *et al.*, 1989; Quast & Cook, 1989; Winquist *et al.*, 1989), glibenclamide *per se* may be a vasoconstrictor. On the other hand, it has been shown that glibenclamide *per se* has no effect on vascular tone *in vitro* or *in vivo* at doses that block the effects of cromakalim administration (Buckingham *et al.*, 1989; Quast & Cook, 1989). In these latter studies, however, the *in vivo* effects of glibenclamide were assessed by measuring blood pressure and not vascular resistance (Buckingham *et al.*, 1989; Quast & Cook, 1989). Moreover, since the work by Quast & Cook (1989) was performed in anaesthetized rats, anaesthesia might have altered the response to this substance. Elucidation of the vascular effects of glibenclamide is important since if this substance is shown to be a vasoconstrictor, this would suggest that potassium channels play a role in the control of basal vascular tone. Therefore, the aim of the present study was to examine the effects of glibenclamide administration on the systemic and splanchnic haemodynamics of conscious rats.

Methods

Animals

Sixty-three adult male Sprague-Dawley rats (Charles River Laboratories, Saint-Aubin-Lès-Elbeuf, France) were used in the present study. All rats were caged and allowed free access to food and water until 14–16 h before the study, when food was withdrawn. Protocols performed in this laboratory were approved by the French Agricultural Office in conformity with European legislation for research involving animals.

Protocols

Protocol 1 Eight sets of experiments were carried out to examine haemodynamic responses to: a sulphonylurea alone (glibenclamide or glipizide), a combination of glibenclamide and a potassium channel opener, a combination of glibenclamide and an L-type calcium channel blocker. (1) Haemodynamic values were measured prior to and 20 min after the administration of glibenclamide (20 mg kg^{-1}, i.v. bolus) (Quast & Cook, 1989; Cavero *et al.*, 1989; Buckingham *et al.*, 1989) in 8 rats. Plasma glucose concentrations were measured at the same time as the haemodynamic values; (2) haemodynamic values were measured prior to and 20 min after the administration of the vehicle of glibenclamide in 7 rats; (3) haemodynamic values were measured prior to and 20 min after the administration of glipizide (20 mg kg^{-1}) in 8 rats; (4) haemodynamic values were measured prior to and 10 min after the administration of the potassium channel opener, diazoxide (30 mg kg^{-1}, i.v. bolus) (Quast & Cook, 1989) in 6 rats; (5) haemodynamic values were measured prior to and 10 min after the administration of diazoxide in 6 rats pretreated with glibenclamide (in these animals, diazoxide was given 10 min after the administration of glibenclamide); (6) haemodynamic values were measured prior to and 10 min after the administration of the L-type calcium channel blocker, nicardipine (1 mg kg^{-1}, i.v. bolus) (Guc *et al.*, 1990) in 6 rats; (7) haemodynamic values were measured prior to and 10 min after the administration of nicardipine in 6 rats pretreated with glibenclamide (in these animals, nicardipine was given 10 min after the administration of glibenclamide);

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(8) the last set of experiments was performed to examine whether the haemodynamic response to glibenclamide was related to a central effect of this substance. For this, haemodynamic values were measured prior to and 20 min after the intracerebroventricular administration (Wright *et al.*, 1986) of glibenclamide (1 mg kg^{-1}) in 4 rats.

Protocol 2 This set of experiments was carried out to examine whether the haemodynamic response to glibenclamide was related to cardiovascular reflexes. For this, haemodynamic values were measured prior to and 20 min after the administration of glibenclamide (20 mg kg^{-1}) in 6 rats in which cardiovascular reflexes were suppressed. This suppression was achieved by the administration of a combination of: hexamethonium [three bolus injections (total dose: 15 mg kg^{-1}), followed by a 0.45 mg kg^{-1} min^{-1} infusion throughout the experiment], atropine methyl bromide (0.005 mg kg^{-1} min^{-1} infusion throughout the experiment), the α_1-adrenoceptor blocker, prazosin (1 mg kg^{-1}, i.v.), and the non selective β-adrenoceptor blocker, propranolol (0.4 mg kg^{-1} for 10 min). Glibenclamide was administered 20 min after the start of the hexamethonium infusion.

Protocol 3 Plasma corticosterone concentrations were measured 24 h after surgery in 3 rats to verify whether animals had fully recovered from surgery. In addition, these plasma concentrations were measured in 3 rats which did not undergo surgery.

Haemodynamic measurements

Twenty-four hours before haemodynamic measurements, catheters were inserted under light diethyl ether anaesthesia. A catheter was inserted in a femoral vein to give drugs (see above). Arterial pressure and heart rate were measured using a catheter inserted into a femoral artery. Portal pressure was measured via a catheter inserted into the portal vein. Briefly, the abdomen was opened and a polypropylene catheter (0.7 mm of diameter) was inserted into a small ileal vein and gently advanced to the bifurcation of the superior mesenteric and the splenic veins. The abdominal incision was closed with catgut. The left ventricle was cannulated via the right carotid artery. All catheters were attached to the external vascular walls and then tunneled subcutaneously to the back of the neck. Haemodynamic studies were performed in conscious unrestrained rats. Cardiac index and regional blood flows were measured by the radioactive microsphere method and the reference sample method as previously described (Lee *et al.*, 1985). For the first set of haemodynamic measurements, a precounted aliquot of approximately 60,000, 16 ± 1 μm diameter, ^{141}Ce-labelled microspheres (sp. act. 10 mCi/g; New England Nuclear, Boston, MA), suspended in Ficoll 70 (10% Pharmacia Fine Chemicals AB, Uppsala, Sweden) and Tween 80 (0.01%) and ultrasonically agitated, was injected into the ventricular catheter and flushed with 1 ml of isotonic saline for 45 seconds. During microsphere injection, a reference blood sample was drawn from the catheter in the femoral artery into a motor-driven syringe at 0.8 ml min^{-1} for 1 min. For the set of second haemodynamic measurements, an injection of ^{113}Sn-labelled microspheres was given and the same technique was used. The animal was then killed with an overdose of pentobarbitone sodium. Individual organs were dissected and placed in separate tubes for counting with a gamma-counter (Computer Gamma G 4000; Kontron, Montigny-Le-Bretonneux, France) at energy settings of 70–210 and 280–1000 keV for ^{113}Sn and ^{141}Ce, respectively. Errors due to the spillover of the ^{113}Sn and ^{141}Ce channel were corrected using ^{113}Sn and ^{141}Ce standards. Adequate microsphere mixing was assumed with a difference $<10\%$ between the left and right kidneys. Cardiac index (CI) was calculated by the following formula: CI (ml min^{-1} 100 g^{-1}) = [radioactivity injected (c.p.m./reference blood sample radioactivity (c.p.m.)] × [100/body wt (g)] × 0.8 (ml min^{-1}). Systemic vascular resistance (SVR) was calculated by the following formula: SVR [(dyn s cm^{-5} 100 g) × 10^3] = mean arterial pressure (mmHg) × 80/Cl (ml min^{-1} 100 g^{-1}). Regional blood flows were calculated by the following formula: organ blood flow (ml min^{-1} 100 g^{-1}) = [organ radioactivity (c.p.m.)/radioactivity injected (c.p.m.)] × Cl (ml min^{-1} 100 g^{-1}). Portal tributary blood flow was calculated as the sum of stomach, intestine, colon, spleen, and mesenteric-pancreas blood flows. Portal territory vascular resistance (PTVR) was calculated by the following formula: PTVR [(dyn s cm^{-5} 100 g) × 10^3] = [mean arterial pressure (mmHg) − portal pressure (mmHg)] × 80/portal tributory blood flow (ml min^{-1} 100 g^{-1}). Hepatic artery vascular resistance (HAVR) was calculated by the following formula: HAVR [(dyn s cm^{-5} 100 g) × 10^5] = mean arterial pressure (mmHg) × 80/hepatic artery blood flow (ml min^{-1} 100 g^{-1}).

Other measurements

Arterial (femoral artery) plasma glucose concentrations were measured by a glucose oxidase method (Trinder, 1969). Plasma corticosterone concentrations were determined in duplicate by a radioimmunoassay method using rabbit polyclonal antibodies (Aupetit-Faisant *et al.*, 1993).

Drugs

Glibenclamide and diazoxide were purchased from Sigma Chemical (St. Louis, MO, U.S.A.). Nicardipine was purchased from Sandoz Laboratory (Division Sandoz, Laboratoires Sandoz S.A.R.L., Rueil-Malmaison, France). Thirty mg of glibenclamide was dissolved in 1 ml 0.1 N NaOH + 4 ml 5% dextrose. Thirty mg of diazoxide was dissolved in 300 μl *N,N*-dimethyl-formamide. Ten mg of nicardipine was diluted in 10 ml of sterile water (pH 3.5).

Statistical analysis

Values are expressed as the means ± s.e.mean. Results were analyzed by one-way analysis of variance. $P<0.05$ was considered significant.

Results

Twenty-four hours after surgery, plasma corticosterone concentrations were 184 ± 7 ng ml^{-1}. These concentrations were 190 ± 17 ng ml^{-1} in animals which did not undergo surgery. At the time of haemodynamic studies rats weighed 321 ± 7 g. Glibenclamide alone significantly decreased the cardiac index (17%) and hepatic artery blood flow (43%) while it increased systemic vascular resistance (31%), portal territory vascular resistance (35%) and hepatic artery vascular resistance (114%) (Table 1). Plasma glucose concentrations were not significantly affected by glibenclamide administration [1.04 ± 0.02 g l^{-1} (i.e., 5.8 ± 0.1 mmol l^{-1}) and 1.16 ± 0.09 g l^{-1} (i.e., 6.4 ± 0.5 mmol l^{-1}) before and after glibenclamide, respectively]. The vehicle did not change systemic and regional haemodynamics (Table 1).

Diazoxide alone significantly increased cardiac index and significantly decreased arterial pressure, and systemic and hepatic artery vascular resistances (Table 2). In rats which received a combination of glibenclamide and diazoxide, arterial pressure, cardiac index, systemic and hepatic artery vascular resistances did not change (Table 2).

Nicardipine alone significantly increased cardiac index and significantly decreased arterial pressure, and systemic and portal territory vascular resistance (Table 3). In rats which received a combination of glibenclamide and nicardipine the cardiac index significantly increased while arterial pressure and systemic vascular resistance significantly decreased (Table 3).

In rats with suppressed cardiovascular reflexes, gliben-

Table 1 Effects of glibenclamide or vehicle on haemodynamics in conscious normal rats

	Glibenclamide ($n = 8$)		*Vehicle* ($n = 7$)	
	Baseline	*After*	*Baseline*	*After*
Heart rate (beats min^{-1})	381 ± 12	371 ± 9	390 ± 10	407 ± 11
Mean arterial pressure (mmHg)	103 ± 2	107 ± 4	100 ± 3	104 ± 4
Cardiac index (ml min^{-1} 100 g^{-1})	28.1 ± 2.5	22.9 ± 2.3*	31.5 ± 3.1	31.5 ± 2.7
Stroke volume index (μl 100 g^{-1})	74 ± 6	62 ± 6*	80 ± 7	77 ± 5
Systemic vascular resistance (10^3 × dyn s cm^{-5} 100 g)	308 ± 30	393 ± 32*	267 ± 23	274 ± 20
Portal tributary blood flow (ml min^{-1} 100 g^{-1})	4.6 ± 0.6	3.6 ± 0.4	6.0 ± 0.8	5.3 ± 0.6
Portal territory vascular resistance (10^3 × dyn s cm^{-5} 100 g)	1875 ± 247	2379 ± 229*	1339 ± 172	1539 ± 159
Hepatic artery blood flow (ml min^{-1} 100 g^{-1})	1.33 ± 0.32	0.65 ± 0.15*	1.37 ± 0.38	1.34 ± 0.28
Hepatic artery vascular resistance (10^5 × dyn s cm^{-5} 100 g)	104 ± 29	179 ± 34*	81 ± 18	77 ± 13

Values are means ± s.e. Animals received 20 mg kg^{-1} glibenclamide (i.v. bolus). Vehicle contained 0.1 N NaOH and 5% dextrose.
*Significantly different from baseline: $P < 0.05$.

Table 2 Effects of diazoxide or glibenclamide plus diazoxide on haemodynamics in conscious normal rats

	Diazoxide ($n = 6$)		*Glibenclamide + diazoxide* ($n = 6$)	
	Baseline	*After*	*Baseline*	*After*
Heart rate (beats min^{-1})	367 ± 10	541 ± 30*	406 ± 21	425 ± 12
Mean arterial pressure (mmHg)	101 ± 3	80 ± 2*	111 ± 3	112 ± 3
Cardiac index (ml min^{-1} 100 g^{-1})	24.3 ± 1.6	37.5 ± 1.7*	22.8 ± 1.0	22.6 ± 1.9
Stroke volume index (μl 100 g^{-1})	66 ± 4	71 ± 7	57 ± 4	53 ± 4
Systemic vascular resistance (10^3 × dyn s cm^{-5} 100 g)	339 ± 27	173 ± 12*	386 ± 15	405 ± 19
Portal tributary blood flow (ml min^{-1} 100 g^{-1})	5.4 ± 0.5	5.7 ± 0.7	5.0 ± 0.4	3.4 ± 0.5*
Portal territory vascular resistance (10^3 × dyn s cm^{-5} 100 g)	1483 ± 211	1067 ± 162	1691 ± 171	2741 ± 325*
Hepatic artery blood flow (ml min^{-1} 100 g^{-1})	1.23 ± 0.12	1.54 ± 0.13	0.86 ± 0.26	0.66 ± 0.17
Hepatic artery vascular resistance (10^5 × dyn s cm^{-5} 100 g)	72 ± 7	43 ± 4*	147 ± 32	177 ± 36

Values are means ± s.e. Doses were 20 mg kg^{-1} (i.v. bolus) for glibenclamide and 30 mg kg^{-1} (i.v. bolus) for diazoxide.
*Significantly different from baseline: $P < 0.05$.

Table 3 Effects of nicardipine or glibenclamide plus nicardipine on haemodynamics in conscious normal rats

	Nicardipine ($n = 6$)		*Glibenclamide + nicardipine* ($n = 6$)	
	Baseline	*After*	*Baseline*	*After*
Heart rate (beats min^{-1})	387 ± 18	524 ± 29*	377 ± 12	534 ± 30*
Mean arterial pressure (mmHg)	109 ± 4	84 ± 4*	112 ± 4	75 ± 4*
Cardiac index (ml min^{-1} 100 g^{-1})	32.7 ± 1.5	46.3 ± 6.3*	24.3 ± 0.9	35.8 ± 2.6*
Stroke volume index (μl 100 g^{-1})	85 ± 4	90 ± 13	65 ± 4	67 ± 3
Systemic vascular resistance (10^3 × dyn s cm^{-5} 100 g)	270 ± 16	153 ± 14*	373 ± 27	171 ± 9*
Portal tributary blood flow (ml min^{-1} 100 g^{-1})	4.7 ± 0.3	6.1 ± 0.9	4.9 ± 0.7	3.7 ± 0.6
Portal territory vascular resistance (10^3 × dyn s cm^{-5} 100 g)	1816 ± 183	1074 ± 141*	1902 ± 284	1580 ± 251
Hepatic artery blood flow (ml min^{-1} 100 g^{-1})	1.28 ± 0.39	1.46 ± 0.22	0.90 ± 0.09	1.00 ± 0.07
Hepatic artery vascular resistance (10^5 × dyn s cm^{-5} 100 g)	101 ± 24	49 ± 5	105 ± 12	61 ± 4

Values are means ± s.e. Doses were 20 mg kg^{-1} (i.v. bolus) for glibenclamide and 1 mg kg^{-1} (i.v. bolus) for nicardipine.
*Significantly different from baseline: $P < 0.05$.

Table 4 Effects of glibenclamide on haemodynamics in conscious rats in which cardiovascular reflexes were suppressed ($n = 6$)

	Baseline	*After glibenclamide*
Heart rate (beats min^{-1})	400 ± 8	311 ± 16
Mean arterial pressure (mmHg)	77 ± 4	92 ± 2*
Cardiac index (ml min^{-1} 100 g^{-1})	31.0 ± 1.6	28.6 ± 1.4*
Stroke volume index (μl 100 g^{-1})	100 ± 4	93 ± 4
Systemic vascular resistance (10^3 × dyn s cm^{-5} 100 g)	201 ± 10	261 ± 11*
Portal tributary blood flow (ml min^{-1} 100 g^{-1})	4.8 ± 0.2	4.1 ± 0.3*
Portal territory vascular resistance (10^3 × dyn s cm^{-5} 100 g)	1209 ± 70	1724 ± 135*
Hepatic artery blood flow (ml min^{-1} 100 g^{-1})	1.96 ± 0.15	0.63 ± 0.13*
Hepatic artery vascular resistance (10^5 × dyn s cm^{-5} 100 g)	32 ± 2	143 ± 26*

Values are means ± s.e. Animals received 20 mg kg^{-1} glibenclamide (i.v. bolus) and were pretreated with a combination of hexamethonium (15 mg kg^{-1} i.v. bolus + 0.45 mg kg^{-1} min^{-1} infusion), methyl atropine bromide (0.005 mg kg^{-1} min^{-1}), prazosin (1 mg kg^{-1} min^{-1} i.v. bolus), propranolol (0.4 mg min^{-1} for 10 min).
*Significantly different from baseline: $P < 0.05$.

Table 5 Effects of intracerebroventricular administration of glibenclamide on haemodynamics in conscious rats ($n = 4$)

	Baseline	*After glibenclamide*
Heart rate (beats min^{-1})	385 ± 10	395 ± 10
Mean arterial pressure (mmHg)	111 ± 8	112 ± 6
Cardiac index (ml min^{-1} 100 g^{-1})	26.5 ± 1.6	27.5 ± 1.8
Stroke volume index (μl 100 g^{-1})	69 ± 5	70 ± 5
Systemic vascular resistance (10^3 × dyn s cm^{-5} 100 g)	339 ± 36	333 ± 36
Portal tributary blood flow (ml min^{-1} 100 g^{-1})	3.8 ± 0.4	3.3 ± 0.2
Portal territory vascular resistance (10^3 × dyn s cm^{-5} 100 g)	2349 ± 480	2581 ± 235
Hepatic artery blood flow (ml min^{-1} 100 g^{-1})	1.46 ± 0.32	1.87 ± 0.20
Hepatic artery vascular resistance (10^5 × dyn s cm^{-5} 100 g)	70 ± 14	50 ± 4

Values are means ± s.e. Animals received 1 mg kg^{-1} glibenclamide.

Table 6 Effects of glipizide on haemodynamics in conscious rats ($n = 8$)

	Baseline	*After glipizide*
Heart rate (beats min^{-1})	364 ± 13	359 ± 15
Mean arterial pressure (mmHg)	95 ± 3	110 ± 5*
Cardiac index (ml min^{-1} 100 g^{-1})	39.4 ± 3.2	35.2 ± 3.8
Stroke volume index (μl 100 g^{-1})	108 ± 8	101 ± 12
Systemic vascular resistance (10^3 × dyn s cm^{-5} 100 g)	205 ± 21	277 ± 37*
Portal tributary blood flow (ml min^{-1} 100 g^{-1})	7.7 ± 0.7	6.7 ± 0.8
Portal territory vascular resistance (10^3 × dyn s cm^{-5} 100 g)	1070 ± 188	1366 ± 185*
Hepatic artery blood flow (ml min^{-1} 100 g^{-1})	0.97 ± 0.18	0.46 ± 0.07*
Hepatic artery vascular resistance (10^5 × dyn s cm^{-5} 100 g)	102 ± 20	223 ± 34*

Values are means ± s.e. Animals received 20 mg kg^{-1} glipizide (i.v. bolus).
*Significantly different from baseline: $P < 0.05$.

clamide significantly decreased cardiac index, portal tributary blood flow and hepatic artery blood flow while it significantly increased arterial pressure and vascular resistance in the portal, hepatic artery, and systemic territories (Table 4).

Intracerebroventricular administration of glibenclamide did not significantly change regional and systemic haemodynamics (Table 5).

Glipizide administration significantly increased arterial pressure (16%) and vascular resistance in systemic, portal, and hepatic artery territories (35%, 35% and 149%, respectively) (Table 6).

Discussion

This study examined the haemodynamic responses to glibenclamide administration in conscious rats. These animals had fully recovered from surgery since they had no increase in plasma corticosterone concentrations. This result confirms previous findings which showed that normal rats had fully recovered from surgery 24 h after the operation (Fenoy *et al.*, 1989; Harrison-Bernard *et al.*, 1991). The finding that plasma glucose concentrations were not altered following glibenclamide differs from previous results which showed that a same dose of this substance induced hypoglycaemia (Quast & Cook, 1989). Since the vehicle of glibenclamide contained glucose in the present study, and not in the previous one, the discrepancy between the studies might be related to the composition of the vehicle. On the other hand, glibenclamide induced systemic vasoconstriction but did not increase arterial pressure. The lack of vasopressor effect was due to a decrease in cardiac index (related to a reduction in stroke volume). These findings show that arterial pressure alone cannot be used to assess the vasoconstrictor effect of glibenclamide.

Glibenclamide elicited hepatic arterial vasoconstriction, which, in turn caused a decline in hepatic arterial blood flow. In addition, this substance induced a vasoconstriction in the portal territory which elicited a decrease in portal tributary blood flow. This decrease, however, was not significant.

Since the suppression of cardiovascular reflexes did not abolish glibenclamide-induced systemic and splanchnic vasoconstriction, the vasoconstrictor action of this substance does not appear to be due to an indirect mechanism, i.e., a reflex increase in sympathetic vascular tone. On the other hand, the intracerebroventricular administration of glibenclamide did not alter systemic and regional vascular resistance. Thus, the vasoconstrictor effect of intravenous glibenclamide was not due to an interaction of this substance with central mechanisms which control the cardiovascular system. Taken together, these findings show that glibenclamide elicited vasoconstriction by acting directly on vessels. In fact, this substance has been shown to block vascular potassium channels directly (Standen *et al.*, 1989; Antoine *et al.*, 1992), a result that is confirmed in the present study, and in a previous one (Clapham *et al.*, 1991), by the finding that glibenclamide abolished the vasodilator effect of an opener of vascular potassium channels, diazoxide, but not that of a L-type calcium channel blocker, nicardipine. Consequently, glibenclamide-induced vasoconstriction appears to be the result of the blockade of vascular potassium channels. This view is also supported by the results which showed that glipizide, another sulphonylurea which blocks vascular potassium channels, induced a systemic and splanchnic vasoconstriction. This last result shows that vasoconstriction was not an idiosyncratic action by glibenclamide.

In the pancreatic β-cell, the blockade of potassium channels (i.e., reduction of potassium efflux from the cell) by glibenclamide induces membrane depolarization (Ashcroft, 1988; Boyd, 1992) which then activates L-type calcium channels and allows calcium to enter the cell (Boyd, 1992). A similar mechanism may occur in the smooth muscle cells and account for glibenclamide-induced vasoconstriction. Indeed, membrane depolarization should occur in smooth muscle cells since glibenclamide blocks vascular potassium channels (see above). In addition, glibenclamide administration seems to be associated with the opening of vascular L-type calcium channel since blockade of these channels by dihydropyridines suppressed the vasoconstrictor action of the sulphonylurea in the present study.

Since glibenclamide-induced vasoconstriction was due to a blockade of potassium efflux from the smooth muscle cells, this suggests that under baseline conditions a potassium efflux was responsible for a certain degree of vasorelaxation. In other words, the results of the present study support the existence of a baseline vasodilator tone which is related to the opening of glibenclamide-sensitive potassium channels.

In conclusion, the present study shows that the blockage of potassium channels by glibenclamide induces a vasoconstriction in the systemic and splanchnic territories. These findings suggest that under baseline conditions the opening of glibenclamide-sensitive potassium channels might be responsible for vasodilator tone.

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