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Impaired K_{ATP} channel function in the fetoplacental circulation of patients with type 1 diabetes mellitus

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Objective: The increased perinatal morbidity in diabetes may be partly related to vascular dysfunction. Because potassium channels play an important role in the regulation of vascular tone, this study explores the impact of diabetes on potassium channel function in the fetoplacental vascular bed.

Study design: Vascular potassium channel function was investigated by ex vivo dual perfusion of isolated placental cotyledons (n = 47). Appropriate control experiments were carried out to exclude nonspecific effects.

Results: Glibenclamide (K_{ATP} channel blocker) increased perfusion pressure to a maximum fetoplacental arterial pressure of 37 ± 6 mm Hg in controls versus 15 ± 6 mm Hg in diabetes ($P < .05$). 4-Aminopyridine (K_V channel blocker) equally increased fetoplacental arterial pressure in controls, and in diabetes (21 ± 4 mm Hg vs 22 ± 2 mm Hg). Apamin and charybdotoxin (K_{Ca} channel blockers) caused a negligible rise in fetoplacental arterial pressure.

Conclusion: In the fetoplacental circulation, K_{ATP} channels and K_V channels significantly contribute to baseline vascular tone. In diabetes, vascular K_{ATP} channel function is impaired.

In diabetes, pregnancy is associated with an increased risk for perinatal complications,[1] including fetal death. Theoretically, these complications can be explained by changes in the fetoplacental circulation, as vascular dysfunction may compromise optimal oxygenation of the vital organs of the fetus. Diabetes is known to affect vascular function, in both macro- and microcirculation. In particular, endothelial dysfunction is a rather common finding in diabetes.[2-4] Although the exposure to the diabetic environment is limited to the duration of pregnancy, previous experiments have shown that this period is sufficient to induce functional changes in the fetoplacental vasculature.[5,6]

The endothelium plays a pivotal role in the maintenance of baseline vascular tone. In diabetes, endothelial

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dysfunction, in particular with respect to the nitric oxide negative (NO) and the cyclooxygenase pathways, have been observed in different vascular beds including fetoplacental arteries.[5,6] Apart from this, recent research points toward an impaired release of endothelium-derived hyperpolarizing factor (EDHF) in diabetes.[7] Opening of the vascular smooth muscle K_{Ca} channel seems to be a final common pathway in the mechanism of action of EDHF. Independent from the EDHF pathway, diabetes has been associated with dysfunction of the cardiovascular K_{ATP} channel, an ion channel that has an important role in the regulation of vascular tone during ischemia.[8]

We hypothesize that vascular potassium channel function in the fetoplacental circulation is compromised in diabetes. To address this hypothesis, we assessed the vasoconstrictor response to potassium channel blockers in the fetoplacental vascular bed in diabetes versus controls.

Material and methods

Study population

Pregnant women with type 1 diabetes were eligible to participate. Controls were healthy pregnant women with uncomplicated pregnancies. Exclusion criteria for both groups were multiple pregnancy, premature birth (<37 weeks' gestation), retained placenta, pregnancy-induced hypertension (diastolic pressure >90 mm Hg on 2 following occasions), and preeclampsia or HELLP syndrome (hemolysis, elevated liver enzymes and low platelets).

From all participants maternal and umbilical venous blood samples for insulin and C-peptide assay were taken within 15 minutes after delivery. All women gave written informed consent. The local medical ethics committee approved this study.

Classification of diabetes mellitus in pregnancy

In pregnancy, diabetes mellitus is classified according to the White Classification. This classification consists of 7 groups: A, B, C, D, F, R, and H. Group A is the classification for gestational diabetes mellitus. Groups B, C, D, F, R, and H are classifications for pregestational diabetes mellitus. In groups B, C, and D, the age of onset of diabetes mellitus in years (>20, 10-19, and <10, respectively), and duration of the disease in years (<10, 10-19, >20) determine the classification. Groups B and C are not associated with vascular complications; group D is associated with a benign nephropathy. In groups F, R, and H, vascular complications determine the classification. Group F is associated with nephropathy, group R with retinopathy, and group H with heart disease.

Cotyledon perfusion

Over a period of 2 years, all placentas from women with type 1 diabetes were obtained immediately after delivery and transported to the laboratory within 10 minutes after delivery. Controls matched for mode of delivery, parity, and maternal age were acquired throughout this period. After arrival at the laboratory, a suitable cotyledon was selected from the placenta for ex vivo dual perfusion as described extensively previously.[6] With a constant fetal arterial inflow, the fetoplacental arterial pressure was considered to be a reflection of net downstream fetoplacental vascular resistance. The contribution of 4 different vascular potassium channels to baseline fetoplacental vascular tone was investigated by adding increasing concentrations of the selective blockers for these channels both in control and in diabetic placentas. These blockers were as follows: glibenclamide for the ATP-dependent K channel (K_{ATP} channel); apamine for the small conductance K_{Ca2+} channel (SK channel); charybdotoxin for the intermediate conductance K_{Ca2+} channel (IK channel), large conductance K_{Ca2+} channel (BK channel), and some voltage-dependent K channels (K_V channel); and 4-aminopyridine for the K_V channel. These blockers were added in 6 to 9 cumulative log-dose steps in concentration ranges from (log concentration [mol/L]): −8.0 to −3.5 (glibenclamide), −9.0 to −6.0 (apamin), −10.0 to −7.0 (charybdotoxin), and −7.5 to −3.5 (4-aminopyridin).

Control experiments on vascular compliance of isolated resistance arteries

To assess the elasticity of the resistance arteries (compliance) of control and diabetic placentas, fetoplacental resistance arteries were isolated from 4 healthy and 4 diabetic patients. On isolation, all arteries were transferred to the 10-mL pressure myograph organ bath, where they were immersed in Ca-free medium as described previously by Smits et al.[9] The artery was gradually pressurized to 50 mm Hg in a pressure myograph (Danish MyoTech P100) over a period of 5 minutes, and the arterial diameter was studied by stepwise increasing the intraluminal pressure from 1 to 60 mm Hg for a period of 2 minutes at each pressure step. This was done twice in succession for each artery. The vessel diameter values for these 2 series were then averaged for each pressure. In this way, 2 or 3 arteries were studied per placenta. These vessel diameter values were averaged to one representative value for each placenta. All preparations were gassed with 95% o_2/5% co_2 to maintain pH at 7.4 throughout the experiment.

Control experiments on morphometry of the fetoplacental arterial circulation

To quantify the vascular diameters and wall thickness we used the computerized image analysis system (eg, Vidas PLUS system, Carl Zeiss GmbH, Jena, Germany).[10] To perform this analysis, the vascular endothelial CD34 antigen was detected by the monoclonal

Table I Clinical characteristics of the participants (median and range)

	Control	Diabetic women
Number of women/placentas	19	18
Number of cotyledons tested	26	21
Maternal age (y)	33.1 (25.0-40.1)	30.5 (21.0-38.2)
Parity (n)	1 (0-3)	1 (0-3)
Gestation (wks)	40 (38-42)	38 (37-39)*
Vaginal delivery (n)	14	13
CS + locoregional anesthetic	4	5
CS + general anesthetic (n)	1	0
Birth weight (g)	3097 (2555-3970)	3525 (2435-4875)
Placental weight (g)	548 (370-700)	670 (400-950)*
Body mass index (kg/m^2)	23.0 (17.7-26.8)	23.9 (17.2-45.9)
Diastolic BP (mm Hg)†	79 (60-90)	87 (55-90)*
Smokers (n)	1	2
White class	—	9 B, 6 C, 1 D, 1 F, 1
HbA1c 1st trimester (%)‡	—	6.5 (5.8-8.8)
HbA1c 3rd trimester (%)‡	—	6.5 (4.8-7.1)
Insulin (mE/mL) maternal umbilical	15.5 (0.2-161.0)	22.0 (5.0-59.0)
	10.0 (5.0-54.0)	52.0 (5.0-242.0)*
C-peptide (nmol/L) maternal umbilical	1.02 (0.16-2.35)	0.12 (0.00-0.48)*
	0.50 (0.21-6.00)	0.26 (0.28-4.16)*

CS, Cesarean section; *BP,* blood pressure.

* $P < .05$ vs healthy controls.

† Diastolic BP was measured 0-6 days before delivery.

‡ Normal value for HbA1c in our laboratory is 4.2%-6.3%; in patients with diabetes is aimed at a value <7.2%.

mouse-anti-CD34 antibody (QBEnd).[10] The Vidas PLUS system is organized in such way that it is able to discriminate the CD34-stained endothelium from the surrounding tissue. In 25 images of each placenta, the following vascularization variables were calculated by the computer system: (a) per image: vascular area as a percentage, vascular perimeter, and vascular number; and (b) per vascular element: the area, the perimeter, and the diameter.

Materials

Apamine, 4-aminopyridine, and H_2O_2 were obtained from Sigma (St. Louis, Mo), charybdotoxin was obtained from Alomone Laboratories (Jerusalem, Israel), glibenclamide was obtained from Hoechst Marion Roussel/Aventis (Bridgewater, NJ). Formalin was obtained from JTBaker (Deventer, The Netherlands), QBEnd was obtained from Biogenex (San Ramon, Calif), and horse antimouse and the ABC Elitekit were obtained from Vector Laboratories (Burlingame, Calif). Before each experiment the blockers were dissolved in Krebs-Henseleit buffer to a solution of 0.8 mmol/L, except for 4-aminopyridine, which was dissolved in water.

Statistical analysis

All data were tested for normality with the Shapiro-Wilk test. Comparison of the clinical characteristics of the diabetic women versus the healthy controls was performed by a Mann-Whitney *U* test. Data on cotyledon perfusion pressures were analyzed with the Prism 3.0 (Graphpad Software, San Diego, Calif) by fitting individual concentration-response curves for each experiment. Maximal percentage changes were calculated by use of the quotient:

$$[\text{max} - \text{baseline fetoplacental arterial pressure}]/\text{baseline fetoplacental arterial pressure} \times 100$$

The resulting parameters did not show Gaussian distribution and were therefore tested by a Mann-Whitney *U* test. Differences were considered to be significant at *P*-values less than .05. Data concerning vascular compliance were compared by paired *t* test. Vidas PLUS data were tested by an unpaired *t* test. All statistics were performed in SPSS (SPSS 10.0, SPSS Inc, Chigaco, Ill).

Results

In total, 37 placentas were included in this study (19 controls, 18 diabetes). When possible, we investigated 2 cotyledons of each placenta simultaneously. In those cases, the 2 cotyledons were used for different series. As such, 26 control cotyledons versus 21 diabetes cotyledons were measured. For the separate potassium channel blocker series, all cotyledons originated from different placentas.

Table I summarizes the clinical characteristics of the participants. Women with diabetes had a shorter gestational

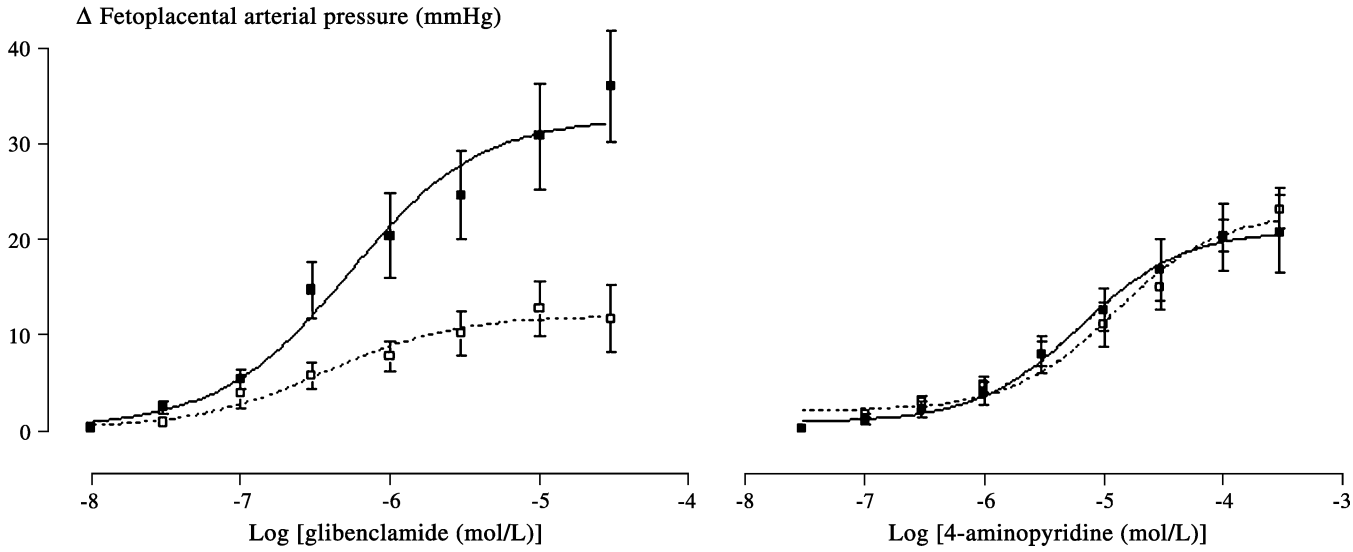

Figure 1 The increase in fetoplacental arterial pressure in response to glibenclamide (*left panel*) and 4-aminopyridine (*right panel*) in the placenta in controls (*solid line*) and in women with diabetes mellitus type 1 (*dotted line*) (mean ± SEM).

Table II Mean ± SEM characteristics of the concentration-response curves for the 4 potassium channel blockers in the fetoplacental circulation

		Fetoplacental arterial pressure (mm Hg)			
Blocker	Group	Baseline	At maximum	Maximum increase	$LogEC_{50}$
Glibenclamide	Control (n = 7)	20 ± 1	56 ± 6	37 ± 6	−6.4 ± 0.2
	Diabetes (n = 6)	23 ± 3	38 ± 4*	15 ± 6*	−6.4 ± 0.2
4-Aminopyridine	Control (n = 7)	22 ± 2	43 ± 4	21 ± 4	−5.2 ± 0.2
	Diabetes (n = 7)	26 ± 2	48 ± 2	22 ± 2	−5.0 ± 0.2
Apamin	Control (n = 6)	27 ± 2	37 ± 3	10 ± 2	−7.4 ± 0.2
	Diabetes (n = 4)	30 ± 3	38 ± 5	9 ± 3	−7.6 ± 0.3
Charybdotoxin	Control (n = 6)	23 ± 3	26 ± 3	4 ± 1	−8.5 ± 0.2
	Diabetes (n = 4)	23 ± 3	24 ± 3	1 ± 1	−10.2 ± 2.1

* $P < .05$ compared with control.

age at time of delivery. As expected, maternal venous C-peptide concentration was lower in diabetic patients versus controls. There was no difference in maternal insulin concentration between controls and patients with diabetes. In umbilical venous plasma, the C-peptide concentration was lower in the patients with diabetes compared with the controls, but as expected, higher than the maternal C-peptide concentrations. In umbilical venous plasma, insulin concentration was increased in patients with diabetes compared with the controls.

Overall, baseline fetoplacental arterial pressure was comparable in controls (n = 19) versus patients with diabetes (n = 18) (22 ± 1 mm Hg vs 24 ± 1 mm Hg, mean ± SEM).

K_{ATP} channel blockade by glibenclamide

Glibenclamide induced a concentration-dependent rise in fetoplacental arterial pressure to a maximum of 56 ± 6 mm Hg in the controls (n = 7) versus 38 ± 4 mm Hg in the patients with diabetes (n = 6) (Table II). As a consequence, the absolute glibenclamide-induced increase in fetoplacental arterial pressure was significantly lower in the patients with diabetes (Figure 1). Figure 2 shows the percentage increments in fetoplacental arterial pressure for all K channel blockers in both groups. This figure also shows the impaired vasoconstrictor response to glibenclamide in patients with diabetes. The $LogEC_{50}$ for glibenclamide was similar in both groups.

K_V channel blockade by 4-aminopyridine

Addition of 4-aminopyridine caused a significant rise in fetoplacental arterial pressure, which was equal in the controls (n = 7) and in the patients with diabetes (n = 7) ($P < .001$) in the controls as well as in the patients with diabetes (Figures 1 and 2). $LogEC_{50}$ was similar in both groups (Table II).

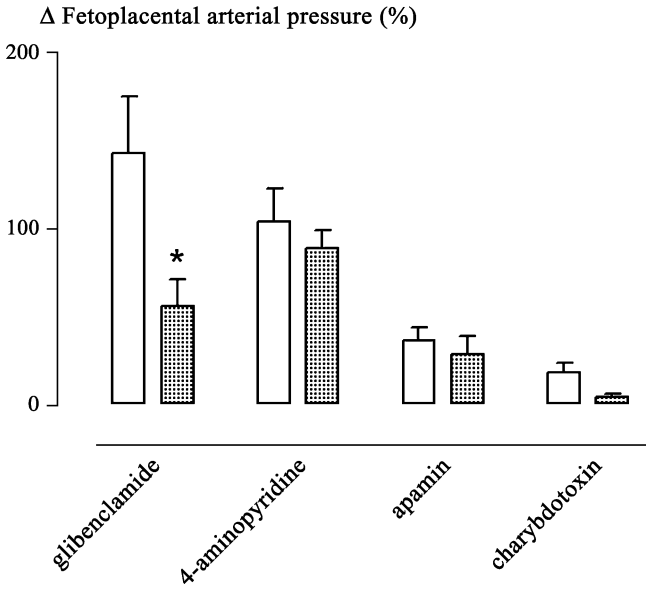

Figure 2 Maximal percentage increase in fetoplacental arterial pressure induced by the highest dose of the different potassium channel blockers in controls (*open bars*) and women with diabetes mellitus type 1 (*dotted bars*) (mean ± SEM). The maximum concentrations given were 0.3 mmol/L for glibenclamide, 1 μmol/L for apamin, 0.1 μmol/L for charybdotoxin, and 0.3 mmol/L for 4-aminopyridin. *$P < .05$ compared with controls.

SK channel blockade by apamine and BK/IK channel blockade by charybdotoxin

Both apamine and charybdotoxin only caused minor increments in fetoplacental arterial blood pressure (Table II, Figure 2), both in the controls (n = 6) and in the patients with diabetes (n = 4).

Comparison of fetoplacental vascular compliance between diabetes and control experiments

In theory, the observed differences between the controls and the patients with diabetes in the response to glibenclamide may relate to diabetes-induced structural changes in the vascular wall. Therefore, fetoplacental vascular compliance was studied.

The diameter at an intraluminal pressure of 0 mm Hg was 90 ± 20 μm in fetoplacental arteries from the controls and 90 ± 3 μm (average ± SEM) in those from the patients with diabetes. The maximum diameter, measured at an intraluminal pressure of 60 mm Hg, averaged 260 ± 35 μm (n = 4) in controls and 270 ± 10 μm (n = 4) in patients with diabetes. The pressure-diameter relationship was similar between the controls and the patients with diabetes. Figure 3 shows the absolute pressure-diameter relationship. The figure for the relative diameter as percentage of the diameter at maximal tested pressure of 60 mm Hg is comparable (not shown).

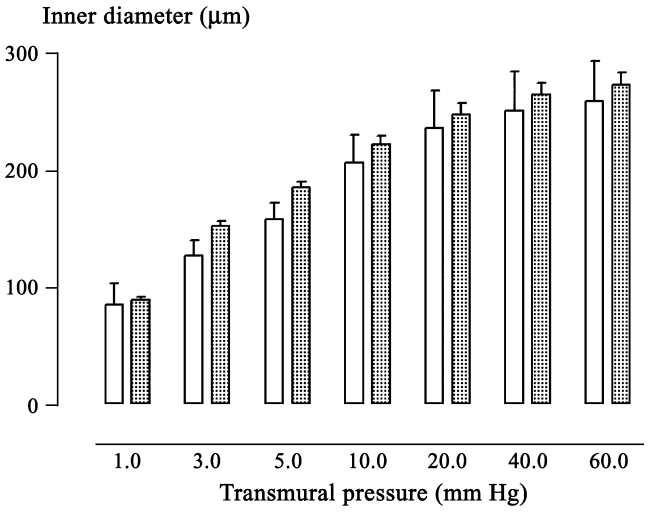

Figure 3 Inner diameter of fetoplacental resistance vessels from healthy controls (*open bars*) and women with diabetes mellitus type 1 (mean ± SEM).

Comparison of placental vascular morphometry between diabetes and control experiments

The impaired vasoconstrictor response to glibenclamide in patients with diabetes may also relate to anatomic differences in the vascular beds between controls and patients with diabetes. Therefore, we performed control experiments on morphometry in placentas from controls (n = 5) and from women with diabetes (n = 8).

The diabetes placentas originated from patients with white class B (n = 2), class C (n = 4), and class D (n = 2). Consequently, none of the women with diabetes had a history of vascular disease. As shown in Table III, all values for the individual vessels were comparable between controls and patients with diabetes.

Comment

The key observation in this study is that the vascular K_{ATP} and K_V channel function significantly contributes to the baseline vascular tone of the ex vivo human fetoplacental circulation. In diabetes, this effect appears to be impaired for the vascular K_{ATP} channel, but not for the vascular K_V channel. Under resting conditions, the K_{Ca} channels hardly contribute to baseline fetoplacental vascular tone, neither in women with diabetes nor in healthy women.

Opening of potassium channels in vascular smooth muscle cells induces vasodilation by hyperpolarizing the cell membrane. By this hyperpolarization, voltage-sensitive calcium channels will close resulting in a fall in calcium influx, a fall in intracellular calcium concentration, and subsequent vasorelaxation. In resting conditions, vascular potassium channels may be open or closed depending on the type of tissue.[11,12] In our setup, the fetoplacental vascular bed shows a clear

Table III Mean (± SEM) of some fetoplacental vascular parameters as calculated by the Vidas PLUS image analysis system in controls and diabetes mellitus

	Healthy controls (n = 8)	Diabetes mellitus type 1 (n = 7)	*P* value
Per field			
Vascular area (%)*	0.18 ± 0.01	0.18 ± 0.01	.90
Perimeter ($\mu m/mm^2$)†	0.064 ± 0.003	0.058 ± 0.005	.32
Vascular count (N/mm^2)‡	960 ± 70	830 ± 130	.39
Per vascular element			
Area (%)	207 ± 23	290 ± 74	.28
Perimeter (μm)	69 ± 4	80 ± 11	.33
Diameter (μm)	8.5 ± 0.4	9.6 ± 1.1	.34

* CD34 positively stained area/total chorionic area × 100.
† Total perimeter of vascular elements/total chorionic area × 10^6.
‡ Total number of vascular elements/mm^2 chorionic area.

vasoconstrictor response to pharmacologic blockade of the K_{ATP} channel by glibenclamide. From these observations, we conclude that the K_{ATP} channel is opened in the ex vivo perfused fetoplacental vascular bed, and contributes to baseline vascular tone. A similar line of reasoning concerns the K_V channel because we observed a relevant vasoconstrictor response to 4-aminopyridine.

Our observation on an impaired function of the vascular K_{ATP} channel in diabetes mellitus is unique as far as the fetoplacental vascular bed is concerned. However, other investigators have observed similar data in other vascular beds in diabetes.[8,12] In theory, the attenuated response to glibenclamide in diabetes may be related to dysfunction of the vascular K_{ATP} channel itself, for example, as a result of glycosylation.

The ATP/ADP ratio is a major determinant of the open state probability of K_{ATP} channels. As such, hypoxia or metabolic stress is a well-known trigger for the opening of K_{ATP} channels. From a theoretical point of view, the vasoconstrictor response to glibenclamide may be explained by the fact that the cotyledon is relatively hypoxic in our perfusion model. An argument against this mechanism is that the perfusion fluid is oxygenated intensively resulting in a P_{O_2} in the inflow perfusion fluid between 400 and 550 mm Hg. However, the tissue oxygenation may be different from normal values, because the perfusion fluid does not contain an oxygen carrier, and we were not able to measure the tissue oxygen content during perfusion. Although previous experiments from our laboratory have shown a constant lactate production in the perfused cotyledon model, this does not imply a hypoxic state because the placenta has been shown to use the glycolysis pathway independent of the oxygen status.[13] Recently, the K_V channel has been shown to play a role in the vasoconstrictor response to hypoxia in the human fetoplacental vascular bed.[14] These investigators observed a hypoxia-induced increase in the perfusion pressure from 27 to 33 mm Hg. In our test with the K_V channel blocker 4-aminopyridine, the perfusion pressure rose from 22 to 43 mm Hg. Because the baseline perfusion pressure was low in our model, and the response to 4-aminopyridine was more pronounced than the reported response to hypoxia, we think that hypoxia could not have played an important role in our setup.

During pregnancy, the fetoplacental vascular bed may be exposed to ischemic insults, which can harm fetal development or even result in fetal death.[15] In theory, the effects of these ischemic periods on the vascular bed might be comparable to those in cardiac and brain tissue. In the latter organs, powerful endogenous mechanisms have been described against ischemic injury, for example, hypoxic vasodilation and ischemic preconditioning,[16,17] both mechanisms that contribute to the optimal match between oxygen use and metabolic demand. The K_{ATP} channel has been shown to play a crucial role in these protective mechanisms.[18] Interestingly, diabetes mellitus has been associated with impaired ischemic preconditioning.[19] Our observation of an impaired vascular K_{ATP} channel function in the fetoplacental vascular bed in patients with diabetes implies that the matching between oxygen supply and demand may be less optimal in these patients. Such a defect may contribute to a poor outcome of ischemic insults in the fetoplacental circulation in patients with diabetes. Along this line of reasoning, the vascular K_{ATP} channel may be an interesting pharmacologic target to improve perinatal morbidity and mortality in women with type 1 diabetes mellitus.

Apart from effects on the vascular smooth muscle cell, potassium channel blockers may affect the endothelium. Studies on the contribution of potassium channels to endothelium-dependent vascular responses in human vessels show that this contribution is small or does not play a role at all.[20,21] As such, the primary site of action of potassium channel blockers is more likely to be the vascular smooth muscle cell than the endothelial cell.

In theory, the impaired vasoconstrictor response to glibenclamide in patients with diabetes might reflect

a more nonspecific defect in vasoconstrictor capacity. However, this seems not to be the case because the vasoconstrictor response to other stimuli (for example, 4-aminopyridine) is similar in patients with diabetes versus in controls. For the NO-synthase inhibitor L-NAME, we previously observed an even more pronounced vasoconstrictor response in patients with diabetes as compared with controls.[6] As such, our observation on an impaired vasoconstrictor response to glibenclamide in patients with diabetes seems to be specific. This conclusion is supported by the fact that our compliance and morphometric studies did not reveal structural differences of the fetoplacental vessels between patients with diabetes and controls.

In 2001 Langer et al[22] presented a study, which concluded that oral treatment with glibenclamide is a clinically effective alternative to insulin for the treatment of gestational diabetes. Our study shows that vascular K_{ATP} channels do have a substantial role in the regulation of baseline fetoplacental vascular tone. Because glibenclamide blocks these K_{ATP} channels, this treatment could compromise placental vascular function. Nevertheless, the transfer of glibenclamide across the human placenta seems to be minimal.[23] Oral treatment with glibenclamide may therefore be expected to only minimally affect fetoplacental vascular function, and as such, may be preferred over other sulfonylurea derivatives, which may cross the placenta.

In conclusion, our human ex vivo study in the fetoplacental vascular bed shows that both the vascular K_{ATP} channel and the K_V channel significantly contribute to the regulation of baseline vascular tone. In type 1 diabetes, the function of the fetoplacental vascular K_{ATP} channel appears to be impaired.

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