Effect of prostacyclin on the perfusion pressure and on the vasoconstrictor response of angiotensin II in the human isolated foetal placental circulation

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The effect of prostacyclin infusion on the perfusion pressure and on the vasoconstrictor response to three doses of angiotensin II was investigated in six full-term human placentas. The placentas were perfused with a modified Krebs-Henseleit solution and placenta perfusion pressure was recorded. Prostacyclin 5×10^{-8} M, infused through the foetal placental circulation, produced a significant decrease in placental vascular resistance. The vaso-depressor effect of prostacyclin persisted throughout the perfusion period and promptly disappeared when the infusion was stopped. The pressor response of angiotensin II was significantly reduced by prostacyclin infusion. These data suggest an interaction between the vascular effects of prostacyclin and angiotensin II on the placental circulation that might be important in the control of foetal placental blood flow.

Keywords prostacyclin angiotensin II human foetal placental circulation

Introduction

Pregnancy is followed by various changes in circulatory homeostasis. Several reports in the literature suggest the importance of prostacyclin and angiotensin II both in normal and in complicated pregnancy. In normal pregnancy there is a decrease in arterial blood pressure (MacGillivray *et al.*, 1969), a reduction in the vasopressor effect of exogenous angiotensin II (Abdul-Karin & Assali, 1961), and an increase in the prostacyclin content of foetal vessels (Remuzzi *et al.*, 1979) and maternal blood (Lewis *et al.*, 1980) in comparison with non-pregnant control subjects.

In complicated pregnancy, women that develop pregnancy-induced hypertension show increased sensitivity to the pressor effect of injected angiotensin II (Gant *et al.*, 1973), and maternal and cord venous concentrations of angiotensin II are significantly elevated (Broughton Pipkin & Symonds, 1977). Remuzzi and collaborators (1980) have shown that prostacyclin production

is depressed in foetal and placental vascular tissue of babies born from mothers with severe pre-eclampsia, and Buossolino and collaborators (1980) reported that in pre-eclampsia there is a reduction of prostacyclin production by maternal blood vessels.

Angiotensin II causes vasoconstriction in isolated umbilicoplacental vasculature (Tulenکو, 1979) and in human foetal placental circulation (Soares de Moura, 1981). Prostacyclin reduces the vasoconstrictor effect of K^+ on isolated perfused human umbilical arteries (Bjoro, 1985); and human umbilical blood-flow is related to prostacyclin production by the umbilical artery (Makila *et al.*, 1983). In order to look for a vascular interaction between angiotensin II and prostacyclin we have studied the effect of prostacyclin on the vasoconstrictor response of angiotensin II on the human isolated foetal placental circulation and also the effect of prostacyclin

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on the basal perfusion pressure of the human isolated foetal placental circulation.

Methods

Six full-term human placentas (480–710 g) were obtained from spontaneous deliveries at the Hospital Geral de Bonsucesso and Hospital Universitário Pedro Ernesto in Rio de Janeiro. Immediately after delivery each placenta was immersed in warm saline to maintain temperature and to prevent drying. A cannula was inserted into each of the umbilical arteries and into the umbilical vein close to the placental plate, and blood was washed out of the vascular tree by gentle injection of 100 to 200 ml of warm Krebs solution containing heparin (Liquemin Roche 0.02 mg ml^{-1}). The two arterial umbilical cannulae were joined by a Y-connector and perfused, at our laboratory, as a single unit, using a pulsatile pump and a modified warm Krebs–Henseleit solution aerated with 95% $\text{O}_2/5\% \text{ CO}_2$. The placental perfusion pressure was measured with a Statham pressure transducer (P23 Db) inserted between the pump and the Y-connector and recorded continuously on a Hewlett-Packard polygraph. The pump frequency in all experiments was fixed at $110 \text{ strokes min}^{-1}$ and the stroke volume was adjusted at the beginning of the experiment to give a mean perfusion pressure of about 30 mm Hg. Placental vascular resistance was derived using the formula: placental perfusion pressure (mm Hg) $\times 100/\text{placental flow (ml min}^{-1})$. For more details of the experimental procedure see Soares de Moura & Solano Vale (1986). Drugs were injected and infused into the rubber tubing close to the arterial cannulas after an equilibration period of 1 h. The following drugs were used: angiotensin II (synthesized by Dr A. C. M. Paiva in the Department of Biophysics, Escola Paulista de Medicina, Brasil) and prostacyclin (Na salt, Upjohn), a gift from Dr F. Ubatuba, Universidade de Brasília, Brasil. Prostacyclin was dissolved in 0.1 M Tris (free base), and kept frozen (-20°C) until shortly before use, when it was diluted with cold Krebs solution. It was infused by means of a constant flow pump (Harvard Mod. 1100) at 0.2 ml min^{-1} . The solution of prostacyclin was prepared according to the volume output of the pulsatile pump of the particular experiment in order to give a final concentration in the perfusion fluid of $5 \times 10^{-8} \text{ M}$. The syringe of the infusion pump was surrounded with plastic bags full of ice, in order to maintain the low temperature of the solution and to limit degradation of prostacyclin.

The data were analysed by two-way analysis of variance and the differences of the pressor responses to three doses of angiotensin II obtained before and during prostacyclin infusion were tested by Newman-Keuls multiple comparison test using an IBM microcomputer, and significance was set as $P < 0.05$. The results are presented as means $\pm$ s.e. mean.

Results

The mean placental perfusion pressure at the beginning of the experiment was $30.3 \pm 2.0 \text{ mm Hg}$ and the mean placental flow was $28.3 \pm 3.1 \text{ ml min}^{-1}$. After the equilibration period, three doses (0.1, 0.3 and 1.0 nmol) of angiotensin II were injected at 15 min intervals, first before and then during the infusion of prostacyclin $5 \times 10^{-8} \text{ M}$. The highest dose (1 nmol) was also injected, shortly after the end of the prostacyclin infusion. In all experiments, prostacyclin produced a vasodilator effect with a mean reduction in placental vascular resistance of $12.1 \pm 3\%$. The mean placental perfusion pressures before, during and after prostacyclin infusion were respectively 29.83 ± 1.1 , 26.2 ± 4.2 and $30.0 \pm 1.0 \text{ mm Hg}$. The hypotensive effect of prostacyclin became evident immediately and persisted throughout the perfusion period.

The three doses of angiotensin II produced before prostacyclin infusion an increase of the placental vascular resistance of 23.5 ± 3.6 , 34.8 ± 4.2 and $48.6 \pm 4.8\%$ respectively. During prostacyclin perfusion, these responses were significantly reduced to 7.7 ± 1.5 , 22.3 ± 2.5 and $32.1 \pm 3.6\%$ respectively. The response to the highest dose of angiotensin II immediately recovered (Figure 1) on discontinuing the prostacyclin infusion.

Discussion

The mechanisms that control human placental blood flow are at the moment not completely understood. The absence of innervation of the human foetal placental vasculature (Baljet & Drukker, 1981) suggests that local and humoral mechanisms must play an important role in the control of blood flow through the foetal placenta. Prostaglandins seem to be involved, since it has been shown that tissues from human umbilical cord arteries and placental veins generate much greater prostacyclin activity than vessels from normal non-pregnant adults (Remuzzi *et al.*, 1979). The findings of Makila *et al.* (1983) that there is a direct association between human

Figure 1 Action of prostacyclin (PGI_2) on the perfusion pressure of the human isolated placenta and on the vasoconstrictor response of angiotensin II (A). Doses of angiotensin II in nmol injected at arrows.

umbilical blood flow and prostacyclin production by umbilical arteries also suggests that prostacyclin is involved in the control of placental blood flow.

Our results show that human foetal blood vessels respond to prostacyclin with a significant decrease in placental vascular resistance. The vasodilator effect lasts for as long as prostacyclin is present, suggesting absence of tachyphylaxis. The rapid recovery indicates a very short half-life of the injected drug. Because it also diminishes the response to concurrently injected angiotensin II, we postulate that prostacyclin increases human foetal placental blood flow not only by a direct vasodilator effect on the placental vessels, but also indirectly, by attenuating the vasoconstrictor effect of angiotensin II.

Our finding that the pressor effect of angiotensin II is reduced by prostacyclin offers experimental support for the suggestion of Goodman *et al.* (1982) that the refractoriness to angiotensin II found in normal pregnancy (Abdul-Karin & Assali, 1961) might be due to the high levels of prostacyclin that have been reported to occur (Remuzzi *et al.*, 1979).

In eclampsia, as suggested by Speroff (1973), a defective production or loss of response of placental vessels to prostaglandins may be related to utero-placenta ischaemia. However, angiotensin II must be an important factor controlling placental blood flow, since Broughton Pipkin & Symonds (1977) have shown that maternal and

cord venous blood levels of angiotensin II are higher in hypertensive pregnancy than in normal pregnancy. Angiotensin II, one of the most potent vasoconstrictor agents, produces vasoconstriction in the placental vessels (Tulenko, 1979; Soares de Moura, 1981). The present results show that the pressor effect of angiotensin II on human foetal circulation is significantly reduced by prostacyclin. It may be that despite the higher concentration of angiotensin II found in cord blood in normal pregnancy (Godard *et al.*, 1976), a reduction in foetal placental blood flow is prevented by the greater production of prostacyclin by foetal blood vessels (Remuzzi *et al.*, 1979). In contrast, the reduction in prostacyclin production in maternal (Bussolino *et al.*, 1980) and foetal vasculature (Remuzzi *et al.*, 1980) and the increase in maternal and cord venous levels of angiotensin II that occur in hypertensive disease of pregnancy (Broughton Pipkin & Symonds, 1977) could induce a reduction in placental circulation that might be partly responsible for the pathological findings in these complicated pregnancies.

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