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The effect of prostaglandin D_2 on the blood vessels of the perfused isolated cotyledon of the human placenta

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Prostaglandin D_2 was shown to constrict the blood vessels of the isolated perfused cotyledon of the human placenta. Its potency was less than that of prostaglandin $F_{2\alpha}$ but similar to prostaglandin E_2. As it is known to dilate uterine blood vessels it may, by its differential action on the foetal and maternal vascular beds, play a role in the local regulation of utero-placental blood flow.

Introduction Prostaglandins that constrict foeto-placental blood vessels and dilate uterine blood vessels may play an important role in the local regulation of utero-placental blood flow (Rankin, 1978). Only one prostaglandin has been found so far to have this differential action, prostaglandin E_2 (PGE_2). Recently however it has been shown that prostaglandin D_2 (PGD_2) is synthesized in human placental tissues and it has been proposed that it too may regulate blood flow in the utero-placental unit (Mitchell *et al.*, 1982). Clark *et al.* (1982) have found PGD_2 dilates uterine blood vessels but as far as we are aware there are no reports as to its action on foetal blood vessels.

In the present study we have examined the vasoactive effects of PGD_2 on the blood vessels of the isolated, dually perfused, cotyledon of the human placenta. We have already shown that this preparation is well suited for studies on vasoactive substances (Abramovich *et al.*, 1983). The resistance of the cotyledonery circulation was monitored under constant arterial flow rates using pressure transducers sited close to the points where the artery and vein supplying a single cotyledon penetrated the chorionic plate. Agonists were introduced into the solution supplied to the foetal vessels and the consequent changes in arterial pressure monitored as a function of time. We have examined the action of PGD_2 relative to controls, and relative to the actions of PGE_2 and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).

Methods Studies were conducted on normal term placentae obtained after vaginal deliveries or Caesarean section operations. The placentae were placed immediately in Krebs solution and were mounted in the perfusion apparatus within 30 min of delivery. The entire apparatus was maintained at 37 ± 1°C. The composition of the Krebs solution was (mM): NaCl 123, $NaHCO_3$ 20, KCl 4.7, $MgSO_4$ 1.19, KH_2PO_4 1.18, $CaCl_2$ 2.53, D-glucose 5.55, Tris HCl 10.1 and Tris base 2.5. In addition the solution used to perfuse the foetal blood vessels contained 30 g l^{-1} dextran (mol. wt. 60,000, Sigma). All solutions were gassed with 95% O_2 and 5% CO_2 and their compositions monitored using a Radiometer PHM73 pH/blood gas analyser. Perfusate pH was maintained in the range 7.33 ± 0.04 and Po_2 (at the point of entry into the placenta) in the range 355 ± 15 mmHg. Foetal perfusion rate was 6.67 ml min^{-1} and the maternal perfusion rate was 17 ml min^{-1}. The absolute pressure across the capillary bed was always less than 60 mmHg and the foetal venous return was always greater than 80% of the arterial supply.

$PGF_{2\alpha}$ and PGE_2 were supplied by Sigma and PGD_2 by Upjohn. The prostaglandins were made up in stock solutions of 2 mg ml^{-1} in ethanol and diluted with Krebs solution to the required concentration immediately before use. The prostaglandins were administered to the foetal arterial supply in volumes if 1 ml by means of a manifold. The drug response was measured as the maximum change in pressure recorded at the arterial transducer following the administration of the drug. One ml volumes of Krebs solution containing ethanol at the same concentration as the prostaglandin samples were used as controls.

Each placenta was used to study the effects of two drugs only. the following protocol was used in each experiment: drug A was administered in the dose sequence 6×10^{-10}, 6×10^{-9}, 6×10^{-8}, 6×10^{-7} mol and about 10 min was allowed to elapse between each response and the next administration. Drug B was then given, following the same procedure. The experiment was completed by repeating the administration of A. Three sets of dose-responses were therefore obtained from each placenta. The sequences A:B:A and B:A:B were used for each pair of drugs examined. Ethanol controls were taken before and after each experiment. In experiments using the sequence A:B:A the mean response to A was compared to B whilst when the sequence B:A:B was used the mean response to B was compared to A.

Table 1 Pressure responses (ΔP) of cotyledonary vessels to prostaglandins D_2 (D), $F_{2\alpha}$ (F) and E_2 (E).

	Response ΔP (mmHg)			
Dose (mol)	*F*	*D*	*ΔFD*	*Placenta*
6×10^{-10}	NR	NR	NR	
6×10^{-9}	0.8±0.4*	0.3±0.3	0.5±0.5	
6×10^{-8}	4.5±0.7***	0.8±0.4*	3.7±0.6***	1 to 6
6×10^{-7}	55.8±13.3***	30.3±10.6**	25.5±10.8*	
Dose (mol)	*E*	*D*	*ΔED*	*Placenta*
6×10^{-10}	NR	NR	NR	
6×10^{-9}	NR	NR	NR	
6×10^{-8}	7.5±3.6	8.8±4.2	−1.3±6.9	7 to 10
6×10^{-7}	42.0±7.1***	51.0±9.4***	−9.0±10.5	
Dose (mol)	*F*	*E*	*ΔFE*	*Placenta*
6×10^{-10}	2.3±1.6	−0.3±0.8	2.6±1.6	
6×10^{-9}	3.1±1.0**	−1.3±1.6	4.4±1.5**	
6×10^{-8}	12.7±3.4***	4.3±5.3	8.3±3.7*	11 to 16
6×10^{-7}	72.4±19.2***	30.2±12.5*	42.3±17.3**	

Columns 2 and 3 show pressure increases over control values and column 4 lists the differential response between the pairs of prostaglandins studied. The values are shown as means obtained from the placentae listed in column 5 ± the standard error of the mean. NR indicates no response was observed in any of the placentae used to construct the mean. The significance of the response over control values, and between differential responses, estimated by a two tailed paired *t* test is indicated as follows: *0.1<P, **0.05<P, ***0.02<P.

Results The placentae studied were divided into three groups each corresponding to a single pair of prostaglandins. Columns 2 and 3 in Table 1 show the mean pressure increases over control values obtained with each group. The ethanol controls produced no detectable effects for the lower three prostaglandin doses and vasoconstrictions in the 1 to 7 mmHg range for the 6×10^{-7} mol dose. There were no obvious differences between prostaglandins with respect to the time course of the responses. Each vasoconstriction produced a relatively rapid rise in arterial pressure followed by a slower decline, the falling phase of the response taking between 5 and 7 times the time of the rising phase. With doses of 6×10^{-7} mol the rising phase took between 1 and 5 min and the falling phase between 7 and 20 min. Column 4 in Table 1 lists the means of the differential responses between the two prostaglandins studied. ΔAB indicates the response of prostaglandin A minus the response of prostaglandin B.

Only vasoconstrictions were observed except when PGE_2 was applied after $PGF_{2\alpha}$ at doses below 6×10^{-7} mol. In about half the cases studied using the latter sequence vasodilatations occurred in the range 1 to 10 mmHg, and in two placentae showed a dose-dependence up to 6×10^{-8} mol.

Discussion Table 1 shows that PGD_2 produces a significant vasoconstriction at a dose of 6×10^{-7} mol and that the threshold dose for a response is about 6×10^{-8} mol. Since Clark *et al.* (1982) have shown that PGD_2 dilates uterine blood vessels, our findings suggest that PGD_2 has the necessary differential action on foetal and maternal vascular beds required for it to function as a local regulator of uteroplacental blood flows (Rankin, 1978). Furthermore PGD_2 is at least as potent a vasoconstrictor of foetal blood vessels as PGE_2; no significant differences were observed between the actions of PGD_2 and PGE_2 in placentae 7, 8, 9 and 10 (Table 1). Owing to the vasodilatations associated with the drug sequence $PGF_{2\alpha}$:PGE_2, the responses of placentae 11–16 showed only marginal significance over controls for PGE_2. It may be noted that Maguire *et al.* (1983) have shown that PGE_2 constricts human placental blood vessels but with less potency than $PGF_{2\alpha}$. Column 4 of Table 1 shows $PGF_{2\alpha}$ tends to produce larger constrictions than either PGD_2 or PGE_2 and that its threshold dose is close to 1×10^{-9} mol, as reported by Maguire *et al.* (1983). We conclude that PGD_2 constricts placental blood vessels with a potency similar to PGE_2 but less than $PGF_{2\alpha}$, and that it may participate in the local regulation of uteroplacental blood flow.

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