PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 162, 187–190 (1979)

Prostaglandin D_2: Effects on the Rabbit Utero-Placental Circulation (40643)[1]

MARGARET K. McLAUGHLIN, TERRANCE M. PHERNETTON, AND JOHN H. G. RANKIN

Departments of Physiology and Gynecology-Obstetrics, University of Wisconsin Medical School and Wisconsin Perinatal Center, Madison General Hospital, Madison, Wisconsin 53715

The role that prostaglandins play as regulators of utero-placental blood flow has been extensively investigated in the past few years (1–4). This work has concentrated on prostaglandins of the E and F series (1–3) and more recently prostacyclin (4). A considerable portion of prostaglandin metabolism *in vivo* may occur via the prostaglandin D pathway rather than prostaglandin E or prostaglandin F (5). This has been demonstrated *in vitro* in both the rat brain and pregnant rat uterus (6, 7). There is little in the literature regarding prostaglandin D's activity in the circulation as it was reported a number of years ago to be a biologically inactive prostaglandin (5). More recent work in the circulation of the kidney and lung has demonstrated that prostaglandin D_2 (8) has similar potency to that of prostaglandins E or $F_{2\alpha}$ (9, 10). We have therefore extended the work involving the role of prostaglandins in the regulation of the utero-placental circulation by examining the utero-placental and renal vascular responses to prostaglandin D_2 in chronically catheterized near-term rabbits.

Materials and methods. Twelve New Zealand white rabbits weighing 2.8–4.8 kg were surgically prepared at 22 ± 2 days gestation. Surgery was performed with intravenous Nembutal (Abbott Laboratories) supplemented with local Xylocaine anesthesia (Astra). A left ventricular polyvinyl catheter (i.d. 0.029 cm) was placed via the carotid artery and two additional polyvinyl catheters were inserted 7–10 cm in each femoral artery. Femoral catheters were threaded subcutaneously to the neck incision and all catheters were filled with heparinized saline, 200 units/ml. The incisions were closed and the catheters were secured under a bandage around the neck. Animals were allowed to recover for at least 24 hr prior to the experimental procedure. The arterial blood pressure of each rabbit was measured with Statham P23Db transducers and recorded with a Beckman R411 recorder. Heart rates were measured from the respective blood pressure tracings using a Beckman cardiotachometer coupler. Individual organ blood flows were determined using the radioactive microsphere technique. Fifteen-micron microspheres with either ^{125}I or ^{141}Ce label (3M Co.) were injected into the left ventricle while withdrawing an integrated arterial blood sample from the femoral catheter at a rate of 2.06 ml/min for 1.5 min. The spheres were suspended in 10% Dextran in saline. Each injection contained approximately 0.5×10^6 spheres at a volume of 0.15–0.20 ml. A stock solution of prostaglandin D_2 was prepared by dissolving 1.0 mg of prostaglandin D_2 in 1 ml of 99% ethanol which was stored at −20°. Appropriate dilutions were made with normal saline just prior to each infusion.

One microsphere injection of either ^{125}I or ^{141}Ce label was made just prior to the intraventricular infusion of prostaglandin D_2 (10 μg/kg/min). Immediately at the end of the 2-min prostaglandin D_2 infusion, another microsphere injection was made, using either ^{125}I- or ^{141}Ce-labeled spheres depending upon which isotope was used for the first microsphere injection. The maternal arterial pressure and heart rate were monitored continuously throughout the experiment. Following a 1-hr recovery period, an intraamniotic fluid catheter was placed, under Nembutal anesthesia, in 6 of the 12 rabbits. The effect of prostaglandin D_2 upon intrauterine pressure was determined by measuring amniotic fluid pressure during the infusion of prostaglandin D_2 (10 μg/kg/min) for 2 min.

Assay. Animals were sacrificed with euthanasia solution upon the completion of the

[1] Supported by Grants HD06736 and HD11187. An abstract of this work was given at the Society for Gynecologic Investigation meetings, March, 1979.

0037-9727/79/090187-04$01.00/0

experiment. The uterus and its contents as well as the kidneys were removed. The placenta for each fetus and its adjacent portion of myometrium were dissected free and each sample placed in a glass counting vial for assay. The kidneys were dissected into approximately 2-g sections and placed in glass counting vials. The integrated arterial blood samples and vials containing the tissue samples were counted on a three-channel Nuclear Chicago 1185 gamma counter and blood flows were calculated using a program on a Univac 1110 computer. Details of this technique have been described previously (11, 12). The resistances of the maternal organs were calculated by dividing the mean maternal arterial pressure (mm Hg) by the blood flow to that organ ((ml/g)/min). Resistance units are therefore expressed as mm Hg × min/ml × g. Results are expressed as the mean ± SE of the mean. Student's *t* test for paired data was used to compare the control and test observations.

Results. The blood flow data obtained in 12 rabbits in response to the prostaglandin D_2 infusion (10 μg/kg/min) are summarized in Table I. There was a small but significant reduction in mean arterial blood pressure from 87 ± 3 to 81 ± 3 mm Hg ($P < 0.01$). There was no change in the maternal heart rate. The uterine blood flow increased in response to prostaglandin D_2 from a mean of 0.14 ± 0.02 to 0.21 ± 0.03 ml/g/min ($P < 0.003$). Uterine vascular resistance decreased from 862 ± 164 to 544 ± 47 mm Hg × min/ml × g ($P < 0.01$). However, in the placenta, the blood flow decreased from 0.32 ± 0.03 to 0.16 ± 0.03 ml/g/min ($P < 0.001$) with a concomitant increase in placental vascular resistance from 389 ± 54 to 1136 ± 337 mm Hg × min/ml × g ($P < 0.03$). Prostaglandin D_2 dilated the renal vasculature. The renal blood flow increased from 4.23 ± 3.7 to 6.02 ± 0.88 ml/g/min ($P < 0.04$). Renal vascular resistance decreased from 23 ± 2.7 to 15.78 ± 1.5 mm Hg × min/ml × g ($P < 0.02$).

TABLE I. THE UTERINE, COTYLEDONARY AND RENAL BLOOD FLOWS, AND VASCULAR RESISTANCES BEFORE (C) AND AFTER (T) A 2-MIN PROSTAGLANDIN D_2 INFUSION (10 μg/kg/min) TO 12 PREGNANT RABBITS

	Blood flow (ml/g/min)		Resistance (mm Hg × min/ml × g)	
Organ	C	T	C	T
Uterus	0.14 ±0.02	0.21 ±0.03	862 ±164	544 ±47
Cotyledons	0.32 ±0.03	0.16 ±0.03	389 ±54	1136 ±377
Kidney	4.32 ±3.7	6.02 ±0.88	23 ±2.7	15.78 ±1.5

In the six rabbits in which amniotic fluid pressure was measured the prostaglandin D_2 infusion caused no change in the intrauterine pressures.

Discussion. The present study demonstrates that the rabbit uterine and placental and renal vasculatures are responsive to exogenously administered prostaglandin D_2. The formation of prostaglandin D_2 from arachidonic acid has been demonstrated in a variety of tissues including dog and rat renal tissue, rat brain, and gastrointestinal and uterine tissue (6, 7, 13, 14).

The circulatory regulatory capabilities of prostaglandin D_2 have only recently been examined. Jones compared the biological activity of prostaglandin D_2 in the sheep circulation to that of prostaglandin $F_{2\alpha}$ and prostaglandin E_2 (15). He found prostaglandin D_2 to have a weak depressor activity at higher doses versus a potent pressor activity at low doses. In addition prostaglandin D_2 exhibited a higher bioactivity than that of prostaglandin $F_{2\alpha}$. In this study we found prostaglandin D_2 to have a mild systemic depressor effect in the pregnant rabbit. No pressor effect was observed in preliminary experiments in which a lower dose of prostaglandin D_2 was utilized. This suggests a species difference in the pressor response which is supported by the observation that exogenous prostaglandin D_2 is a vasodepressor in dogs (16). The possibility also exists that there is modification in the pressor activity of prostaglandin D_2 during pregnancy. Jones (15) found pregnant ewes to be relatively insensitive to the pressor effects of exogenous prostaglandin D_2.

Individual organ responses to prostaglandin D_2 have been examined in the dog kidney and lung (9, 16). Prostaglandin D_2 increases lung airway resistance and increases pulmonary perfusion pressure in the dog, while strongly dilating the renal vasculature. In this study, prostaglandin D_2 dilated the rabbit renal vasculature.

There has been considerable interest in the role that prostaglandins play in utero-placental blood flow regulation. Exogenous prostaglandin $F_{2\alpha}$ is a utero-placental vasoconstrictor in the pregnant sheep (3) while prostaglandin E_2 dilates this vasculature when administered via the fetal compartment (3). Endogenous prostaglandins may be a partial determinant of the normal utero-placental blood flow in the pregnant monkey, rabbit, and sheep as prostaglandin synthetase inhibition results in utero-placental vasoconstriction in all these species (2, 17, 18). In addition to their direct effect on the utero-placental blood flow, prostaglandins appear to be modulators of other vasoactive substances such as angiotensin II and norepinephrine. This has been demonstrated both systemically in the pregnant ewe (19) as well as in the utero-placental circulation of the ewe and monkey (19, 20) and rabbit (2).

The complexity of the prostaglandin synthetic pathway lends itself to a modulatory role as the endproducts of arachidonic metabolism may shift depending upon the needs of the organ (8). In this sense it is important to describe the organ response to a variety of prostaglandins. Prostaglandin D_2 is a potent placental vasoconstrictor while mildly dilating the uterine vasculature. The divergence of response is similar to that noted by Novy *et al.* (21) in the pregnant rhesus monkey. In Novy's experiments, prostaglandin E_2-induced uterine contractions resulted in either no change or an increase in myometrial flow with a marked reduction in placental blood flow. This pattern is identical to the one observed in this study in response to prostaglandin D_2. Novy *et al.* did not discount the possibility that vasomotor regulation of the myometrial arterioles might exist independent of the mechanical force of contraction. The reduction in myometrial resistance observed in our study suggests that the vasomotor changes observed by Novy during labor may indeed be a chemically dependent phenomena especially since prostaglandin levels increase markedly at parturition (22). However, the prostaglandin D_2 levels present during labor are not known. In addition the pregnant rabbit myometrium appears to be insensitive to endogenous vasoactive stimuli. Hypoxia severe enough to cause placental vasoconstriction has little effect on the myometrial vessels (23). The response to prostaglandin D_2 noted here may be due solely to a pharmacologic response with little correlation to a naturally occurring event.

Summary. The uterine, placental, and renal vascular responses to a 2 min intraventricular prostaglandin D_2 infusion (10 μg/kg/min) were examined using the microsphere technique in 12 chronically catheterized near-term rabbits. The prostaglandin D_2 infusion significantly decreased mean arterial pressure from 87 ± 3 to 81 ± 3 mm Hg. Uterine vascular resistance decreased from 862 ± 164 to 544 ± 47 mm Hg × min/ml × g while the placental vascular resistance increased from 389 ± 54 to 1136 ± 337 mm Hg × min/ml × g. The renal vasculature dilated in response to prostaglandin D_2, the renal vascular resistance decreasing from 23 ± 2.7 to 15.8 ± 1.5 mm Hg × min/ml × g. Thus, prostaglandin D_2 dilates the uterine and renal vasculature and is a strong placental vasoconstrictor. This response is independent of intrauterine pressure changes and appears to be a direct effect.

The authors wish to thank Dr. John Pike of the Upjohn Company who supplied the prostaglandin used in these experiments.

1. Terragno, N. A., Terragno, D. A., Pacholcyzk, D., and McGiff, J. C., Nature (London) **57,** 411 (1974).
2. Venuto, R. C., O'Dorisio, T., Stein, J. H., and Ferris, T. F., J. Clin. Invest. **55,** 193 (1975).
3. McLaughlin, M. K., Brennan, S. C., and Chez, R. A., Amer. J. Obstet. Gynecol. **130,** 408 (1978).
4. Rankin, J. H. G., Phernetton, T. M., Anderson, D. F., and Berssenbrugge, A. D., J. Devel. Physiol. **1,** 151 (1979).
5. Nugteren, D. H., and Hazelhof, E., Biochim. Biophys. Acta **326,** 448 (1973).
6. Sun, F., Prostaglandins **14,** 181 (1977).
7. Katori, M., Harada, Y., Yamashita, Y., Ishibashi, M., and Miyazaki, H., Prostaglandins **15,** 697 (1978).
8. Pace-Asciak, C. R., Prostaglandins **13,** 811 (1977).
9. Feigin, L. P., Chapnick, B. M., Flemming, J. E., Flemming, J. M., and Kadowitz, P. J., Amer. J. Physiol. **233,** H573 (1977).
10. Spannhake, E. W., Temen, R. J., Wegmann, M. J., Heymann, A. L., and Kadowitz, P. J., J. Appl. Physiol. **44,** 397 (1978).
11. Buss, D. D., Bisgard, G. E., Rawlings, C. A., and Rankin, J. H. G., Amer. J. Physiol. **288,** 1497 (1975).
12. Mueller, D., Stoehr, B., Phernetton, T., and Rankin, J. H. G., Proc. Soc. Exp. Biol. Med. **159,** 25 (1978).

13. Knapp, H. R., Oelz, O., Sweetman, B. J., and Oates, J. A., Prostaglandins **15,** 751 (1978).
14. Dunn, M. J., and Hood, V. L., Amer. J. Physiol. **233,** F169 (1977).
15. Jones, R. L., *in* "Advances in Prostaglandin and Thromboxane Research" (B. Samuelssen and R. Paoletti, eds.), Vol. 1, p. 221. Raven Press, New York (1976).
16. Wasserman, M. A., DuCharme, D. W., Griffin, R. L., DeGraaf, G. L., and Robinson, F. G., Prostaglandins **13,** 255 (1977).
17. Speroff, L., J. Reprod. Med. **15,** 181 (1975).
18. McLaughlin, M. K., Brennan, S. C., and Chez, R. A., Amer. J. Obstet. Gynecol. **132,** 430 (1978).
19. Berssenbrugge, A., Anderson, D., Phernetton, T., and Rankin, J. H. G., Proc. Soc. Exp. Biol. Med. **159,** 281 (1978).
20. Franklin, G. O., Dowd, A. J., Caldwell, B. V., and Speroff, L., Prostaglandins **6,** 271 (1974).
21. Novy, M. J., Thomas, C. L., and Lees, M. H., Amer. J. Obstet. Gynecol. **122,** 419 (1975).
22. Liggins, G. C., Fairclough, R. J., Grieves, S. A., Kendall, J. Z., and Knox, B. S., *in* "Recent Progress in Hormone Research", Vol. 29, p. 111. Academic Press, New York (1973).
23. Duncan, S. B., J. Physiol. **204,** 421 (1969).

Received February 21, 1979. P.S.E.B.M. 1979, Vol. 162.