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Prostaglandin Concentrations in Ovine Maternal and Fetal Tissues at Late Gestation

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ABSTRACT. Maternal and fetal sheep organs were measured for their concentrations of prostaglandins (PG) E_2, $F_{2\alpha}$, 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM), 6-keto $PGF_{1\alpha}$ (hydrolysis product of PGI_2), and 6-keto PGE_1 (enzymatic product of PGI_2) by radioimmunoassay at day 131 of pregnancy (0.90 gestation). It was observed that the concentrations of PGFM were greater ($p < 0.01$) in maternal endometrium than in any other maternal tissue or any other PG measured in endometrium. The lowest concentrations of PG in maternal tissues were in the myometrium, while PGE_2 and 6-keto $PGF_{1\alpha}$ were present in maternal lungs in high concentrations. Fetal prostaglandin concentrations were high in the chorioallantois, fetal portion of the cotyledons and amnion, while they were very low in the kidney, liver, and lung. Fetal lung concentrations were lower than maternal lung concentrations ($p < 0.01$) for all PG measured. In fetal aorta and ductus arteriosus, 6-keto $PGF_{1\alpha}$ concentrations were significantly greater ($p < 0.05$) than all other measured PG, while in umbilical artery and vein 6-keto $PGF_{1\alpha}$ levels were equal to PGE_2 levels. 6-Keto PGE_1 concentrations were consistently among the lowest in all tissues measured. These results suggest that the endometrium may serve as a metabolic barrier to PG diffusing from the chorioallantois to the myometrium, that the capacity of pulmonary tissue to produce PG may increase with age, that the fetal membranes and cotyledons may be one major source of circulating PG in the fetus, and that 6-keto $PGF_{1\alpha}$ is the major metabolite of PGI_2 in ovine tissues. (*Pediatr Res* 20: 83–86, 1986)

Abbreviations

PG, prostaglandin(s)
6KE, 6-keto PGE_1
PGFM, 13,14-dihydro-15-keto $PGF_{2\alpha}$ $_{6KF,\ 6\text{-keto } PGF1\alpha}$
6KF, 6-keto $PGF_{1\alpha}$

PG contribute to a number of physiological functions in pregnant animals and their fetuses throughout gestation and at parturition (1). These functions include contributions to the regulation of pulmonary, uterine, and placental blood flow; the maintenance of the patency of the ductus arteriosus; the regulation of myometrial contractility and cervical compliance; control of renal blood flow and glomerular filtration rate; and the regulation of fetal breathing movements. Because of the diversity of these physiological roles and the fact that PG generally are locally acting and not circulating hormones, it would be expected that the production and metabolism of individual PG would vary considerably from tissue to tissue.

Other investigators have studied the plasma levels of PG, tissue levels of PG and/or production of PG by tissues, cells and tissue homogenates from maternal and fetal animals at various times of gestation (2–13). However, these studies generally have been concerned with one organ and have not compared PG levels between organs. Moreover, these studies usually measured primary PG and not their metabolites. Information regarding PG metabolites in tissues gives a more complete picture of overall PG formation and degradation. One of these metabolites is 6KE, a biologically active enzymatic derivative of prostacyclin (PGI_2) (14), whose concentrations in ovine tissues have not been measured previously. The purpose of this study, therefore, was to measure primary and metabolic PG levels in a variety of fetal and maternal sheep organs at late pregnancy to gain a more complete regard for the overall control of gestational PG production.

MATERIALS AND METHODS

Animals. Six ewes of mixed breeds at 131 days of gestation (0.90 gestation, term = 145 days) were used. Gestational age was calculated from the time of insemination and verified by the crown-rump length of the fetuses at the time of delivery. Five of the ewes had single pregnancies, and one had a twin pregnancy.

Tissue collection and extraction. The sheep were anesthestized with sodium pentobarbitone (1 g, Abbott Laboratories, Montreal, Canada) and a laparotomy was performed to collect tissues.

The following tissues were collected: maternal—myometrium (principally longitudinal muscle), endometrium, cotyledons, and the basal portion of the middle lobe of the lung; fetal—cotyledons, chorioallantois, amnion, the basal portion of the middle lobe of the lung, kidney (cortex and medulla unseparated), liver, descending aorta (1 cm distal to ductus arteriosus), ductus arteriosus, umbilical artery, and the umbilical vein. The tunica adventitia was not removed from vascular tissue. Tissues were immediately frozen in dry ice-acetone and stored at −20° C until assayed.

Tissues were thawed to 4° C, cleaned of connective tissue, washed free of blood clots in ice-cold 0.154 M NaCl, blotted and weighed. Tissues were each added to 5.0 ml of absolute ethanol and homogenized for 20 s at 4° C with a Brinkman Polytron. The homogenate was centrifuged (10 min, 4° C, 1500 × *g*) and 1.0 ml of the ethanolic extract was withdrawn and dried under N_2. The dried samples were reconstituted in 1.0 ml of 0.05 M phosphate buffer containing 1 mg gelatin/ml. Aliquots of these samples were assayed for PG by radioimmunoassay.

Radioimmunoassays. PG E_2, $F_{2\alpha}$, PGFM, and 6KF (PGI_2

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hydrolysis metabolite) were measured using assays described and characterized elsewhere (9, 11–13, 15, 16). The radioimmunoassay for 6KE is described below.

Preparation of the ^{125}I histamine-6KE conjugate. Histamine was conjugated to 6KE using the procedure of Maclouf *et al.* (17) with slight modifications. Histamine-free base (Sigma Chemical Co., St. Louis, MO) and 1-ethyl-3-(3-dimethylamine-propyl) carbodiimide (Sigma) were each dissolved in water (20 mg/ml). One hundred microliters of each solution were then mixed and the pH adjusted to 6 with 1 N HCl prior to the addition of 6KE. At alkaline pH, 6KE becomes unstable (14). 6KE (2 mg) was dissolved in 100 μl of 50% ethanol, and mixed with the carbodiimide-histamine solution. The pH was adjusted to 5.0 and the solution stored at room temperature overnight. The following day the mixture was chromatographed by thin-layer chromatography on silica gel plates (Whatman LK 6F 5 × 20 cm) and developed in the system n-butanol:acetic acid:water (75:10:25). A small portion of the mixture applied to a second plate was used to visualize the histamine-PG conjugate by spraying with phosphomolybdic acid (Fisher Scientific Co., Fairlawn, NJ) dissolved in ethanol and then heating the plate. The coupled prostaglandin ($R_f = 0.32$) was scraped from the plate and eluted with 90% methanol (3 × 2 ml) and stored at −20° C.

The conjugate was radioiodinated by the chloramine-T method. Briefly, 10 μl of the histamine-6KE conjugate was dried in a conical-shaped 1.5 ml tube and reconstituted in 10 μl of 0.5 M phosphate buffer, pH 7.4. To this was added 10 μl of Na-^{125}I (New England Nuclear, Boston, MA) and then 10 μl of chloramine-T (Eastman Kodak Co., Rochester, NY; 10 mg/ml in phosphate buffer). The reaction proceeded for 30 s and was stopped by addition of 10 μl of sodium metabisulfite (Fisher; 10 mg/ml in phosphate buffer). The reaction mixture was applied to a thin-layer chromatography plate and developed in the system chloroform:methanol:water (80:20:0.5). The iodinated conjugate was visualized using autoradiography ($R_f = 0.77$), scraped from the plate, eluted with 90% methanol (3 × 2 ml) and stored at 4° C.

6KE radioimmunoassay. The antibody to 6KE was developed from antisera raised in rabbits by Dr. L. Levine, Brandeis University, Waltham, MA.

The cross-reactivity of the antisera was determined by the percent mass ratio required to displace 50% of the total radioactive ligand bound. These values are: PGA_1 (1.3%), PGA_2 (0.83%), PGE_1 (1.10%), PGE_2 (3.60%), $PGF_{1\alpha}$ (0.03%), $PGF_{2\alpha}$ (0.02%), TXB_2 (0.03%), 6KF, (0.09%), 6α-carba PGI_2 (prostacyclin analogue, The Upjohn Co., Kalamazoo, MI) (0.07%), PGI_2 Na salt (1.05%), PGE_2 methyl ester (1.8%) and 13,14-dihydro-15-keto PGE_2 (0.05%) and < 0.01% for 15-keto PGE_1, 15-keto PGE_2, 15-keto $PGF_{1\alpha}$, 13,14-dihydro-15-keto PGA_2, and 13,14-dihydro-15-keto $PGF_{2\alpha}$. The sensitivity of the assay is less than 1 pg and the coefficients of variation are 7.6% (intraassay) and 9.7% (interassay). The recovery equation of 6KE added to tissue before homogenization and extraction was determined by Doktorcik and Kennedy (18) and found to be $y = (1.008 \pm 0.036)x + 86.17$ pg (mean slope ± SEM).

Statistical analysis. The data were analyzed by analysis of variance where variation was distributed between prostaglandins and tissues for each animal. Animals were treated as major replications (blocks). To reduce heterogeneous variance, the data were transformed to common logarithms before analysis. When a significant F value was obtained ($p < 0.05$), means were separated using Duncan's New Multiple Range test. The untransformed data are presented in the tables.

RESULTS

Maternal tissues. The concentrations (pg/mg wet weight) of prostaglandins in maternal tissues are listed in Table 1. The concentrations of all PG were lowest in the myometrium ($p < 0.01$). In the myometrium and lung, 6KF levels were greater than all other PG ($p < 0.05$). The endometrium had higher levels of PGFM than any other PG ($p < 0.01$). Moreover, endometrial concentrations of PGFM were greater than in any other tissue ($p < 0.01$). The concentrations of 6KE consistently were lower than all other PG in endometrium and lung.

Fetal tissues. The PG concentrations of fetal tissues are listed in Table 2. The chorioallantois and cotyledons generally had higher levels of PG than other fetal tissues, whereas the lung, liver, and kidney generally had the lowest PG concentrations. Amnion tissue had lower levels of all PG than the cotyledons ($p < 0.05$) and lower values than the chorioallantoic fetal membrane for PG E_2, $F_{2\alpha}$, and 6KF ($p < 0.05$).

Vascular tissue 6KF concentrations were consistently the highest ($p < 0.05$) while concentrations of $PGF_{2\alpha}$, PGFM, and 6KE were very low. PGE_2 concentrations were lower ($p < 0.05$) than 6KF in the ductus arteriosus and the aorta. However, in the umbilical artery and vein, PGE_2 concentrations were equal to those of 6KF. The levels of 6KE were lower than those in 6KF in most tissues, but were equal to those of $PGF_{2\alpha}$ and PGFM in many tissues.

Comparison of maternal and fetal tissues. The concentrations of PG in paired samples from maternal and fetal lungs and cotyledons were compared by analysis of variance. The lung values for each of the twin fetuses were averaged first and then compared with those of their mother. The values for cotyledons from the twin pregnancy were compared for maternal and fetal cotyledon portions of one of the twins. It was observed that for each PG, the concentrations in maternal lung were greater ($p < 0.01$) than in fetal lungs. In cotyledons, there were no significant differences in maternal and fetal concentrations of $PGF_{2\alpha}$, PGFM, or 6KE. Fetal cotyledon concentrations of PGE_2 ($p < 0.01$) and 6KF ($p < 0.05$) were greater than maternal cotyledon concentrations.

DISCUSSION

The results of this study have revealed that considerable differences in the pattern and concentrations of PG exist in fetal and maternal tissues in late gestation sheep. Most notable of these observations are the demonstration of high levels of PGFM in maternal endometrium, the significant differences in pulmonary tissue PG concentrations in maternal and fetal sheep, the relatively high levels of PG in fetal membranes and cotyledons compared to other fetal tissues, and the consistently low concentrations of the prostacyclin metabolite, 6KE.

By immediately freezing the tissue and collecting all uterine

Table 1. *PG concentrations in maternal tissues (mean ± SEM, n = 6)*

Tissue	Prostaglandin (pg/mg tissue)					
	PGE_2	$PGF_{2\alpha}$	PGFM	6KF	6KE	p
Myometrium	4 ± 0^{b} (*b*)	3 ± 1^{b} (*b*)	3 ± 1^{b} (*c*)	12 ± 3^{a} (*c*)	5 ± 1^{b} (*b*)	<0.05
Endometrium	211 ± 107^{b} (*a*)	236 ± 76^{b} (*a*)	834 ± 199^{a} (*a*)	173 ± 52^{b} (*b*)	35 ± 8^{c} (*a*)	<0.01
Cotyledons	339 ± 153^{a} (*a*)	141 ± 27^{ab} (*a*)	229 ± 65^{a} (*b*)	160 ± 41^{a} (*b*)	51 ± 7^{b} (*a*)	<0.05
Lung	608 ± 238^{ab} (*a*)	206 ± 69^{bc} (*a*)	125 ± 32^{cd} (*b*)	1215 ± 393^{a} (*a*)	53 ± 11^{d} (*a*)	<0.05
p	<0.01	<0.01	<0.01	<0.01	<0.01	

Means bearing the same letters are not significantly different: ^{a,b,c,d} within rows; (*a,b,c*) within columns.

Table 2. *PG concentrations in fetal tissues (mean ± SEM, n = 7)*

Tissue	Prostaglandin (pg/mg tissue)					
	PGE_2	$PGF_{2\alpha}$	PGFM	6KF	6KE	*p*
Chorioallantois	1946 ± 779^{a} (*a*)	114 ± 23^{b} (*a*)	21 ± 5^{c} (*b*)	276 ± 53^{b} (*a*)	25 ± 5^{c} (*ab*)	<0.01
Amnion	313 ± 135^{a} (*b*)	34 ± 6^{bc} (*b*)	28 ± 12^{c} (*b*)	72 ± 12^{b} (*b*)	11 ± 2^{c} (*bcd*)	<0.01
Cotyledons	711 ± 146^{a} (*a*)	176 ± 25^{b} (*a*)	130 ± 30^{bc} (*a*)	337 ± 61^{ab} (*a*)	41 ± 6^{c} (*a*)	<0.01
Lung	17 ± 5^{a} (*e*)	10 ± 3^{a} (*c*)	17 ± 8^{a} (*bc*)	22 ± 9^{a} (*c*)	3 ± 1^{b} (*e*)	<0.05
Kidney	26 ± 7^{a} (*de*)	9 ± 2^{b} (*c*)	11 ± 1^{ab} (*bc*)	11 ± 2^{ab} (*c*)	4 ± 1^{b} (*de*)	<0.05
Liver	5 ± 2^{b} (*f*)	6 ± 1^{ab} (*c*)	4 ± 1^{ab} (*cd*)	15 ± 5^{a} (*c*)	10 ± 3^{ab} (*bcd*)	<0.05
Aorta	52 ± 27^{b} (*de*)	11 ± 4^{b} (*c*)	3 ± 1^{c} (*d*)	180 ± 48^{a} (*ab*)	13 ± 4^{b} (*bcd*)	<0.05
Ductus arteriosus	20 ± 7^{b} (*e*)	13 ± 5^{b} (*c*)	4 ± 2^{c} (*d*)	162 ± 58^{a} (*b*)	9 ± 3^{bc} (*cde*)	<0.05
Umbilical artery	105 ± 52^{a} (*cd*)	12 ± 5^{bc} (*c*)	5 ± 2^{bc} (*cd*)	100 ± 28^{a} (*b*)	9 ± 3^{bc} (*cde*)	<0.05
Umbilical vein	170 ± 53^{a} (*bc*)	18 ± 4^{b} (*bc*)	3 ± 1^{c} (*d*)	155 ± 42^{a} (*ab*)	17 ± 4^{b} (*bc*)	<0.01
p	<0.05	<0.05	<0.05	<0.05	<0.05	

Means bearing the same letters are not significantly different: [a,b,c] within rows; (*a,b,c,d,e,f*) within columns.

and fetal membrane tissues from the antimesometrial side of the uterus in the midfundal region, the regional location of the specimen was standardized between sheep, thereby avoiding some of the difficulties in tissue collection as described by others (4, 9, 11). Additionally, the manual separation of the cotyledons into fetal and maternal components is not complete, since some fetal trophoblast (binucleate) cells migrate into maternal tissue (19). Nevertheless, this separation does result in a portion which is mostly maternal in origin and a fetal portion. It is also realized that while measuring the tissue concentration of any PG at a single point in time does not yield specific information about its synthesis, metabolism, and release, it does produce extremely useful information about relative PG production capacities of the tissue as demonstrated by studies using inhibitors of PG synthesis (11).

The high concentrations of PGFM in endometrial tissue suggest high activities of the primary metabolic enzymes of $PGF_{2\alpha}$ and PG, 15-hydroxy prostaglandin dehydrogenase, and 13,14-reductase. Enhanced activity of these enzymes may allow the endometrium to act as a metabolic barrier to PG diffusing between fetal and maternal tissues, much as the chorion may act in human gestation (20–22). Inasmuch as the endometrium is in juxtaposition to the chorioallantois, a tissue with high concentrations of PG, and the myometrium, the site of PG action at term, its capacity to metabolize PG which stimulate uterine contractile activity may be a vital component of the defense mechanism of pregnancy and the maintenance of gestation in sheep.

Pulmonary tissue PG concentrations were greater consistently in mothers than in fetuses. Powell and Solomon (23) showed that the ability of calf fetal lung tissue to convert arachidonic acid to PG increases steadily during gestation and following birth up to adulthood. Similar results from unpublished experiments in sheep were observed also. More recently Printz *et al.* (24) showed that lung cyclooxygenase activity increases in sheep near the end of gestation and increases to adulthood, supporting the earlier findings of Powell and Solomon (23). However, this phenomenon is not universal for all species, as the ability of fetal rabbits to convert arachidonic acid to PGE_2 reached a maximum at day 28 gestation and declined thereafter to adulthood (23). These conclusions in rabbits have been observed also by Simberg and Uotila (25) using perfused rabbit lungs.

The greatest concentation of prostaglandins in fetal tissues is in the fetal membranes (amnion and chorioallantois) and the fetal portion of the cotyledons. Moreover, PGE_2 concentrations were greater in fetal cotyledons than in maternal cotyledons. It is known that fetal plasma PGE_2 and $PGF_{2\alpha}$ concentrations rise during labor in sheep (7, 13) and fall precipitously at birth (7) following clamping of the cord (26). Presumably, since the chorioallantois and fetal cotyledons are perfused with fetal blood and since PG output increases from chorioallantoic cells and cotyledonary cells with the onset of labor in sheep (13), these tissues are major sources of the fetal circulating PG.

6KE is formed from PGI_2 or 6KF by 9-hydroxy PG dehydrogenase (14). Unlike 6KF, 6KE has several biological effects in fetal animals. It is nearly as potent as PGE_2 in stimulating dilation of the ductus arteriosus (27), and it promotes dilation of the pulmonary and systemic vascular beds (28, 29). It has uterine and placental effects similar to those of PGI_2 in that it promotes uterine blood flow, but causes vasoconstriction in maternal and fetal cotyledons (30, 31).

In nonpregnant ovariectomized, estrogen-treated ewes, 6KE promotes myometrial contractility (32). In one experiment, the infusion of 6KE (1.2 μg/kg/min) into the tarsal vein of a fetal lamb dramatically inhibited fetal breathing movements stimulated by the constant infusion of indomethacin (25 mg/kg/day) into the maternal femoral vein (Patrick JE, Olson DM, unpublished observation). 6KE is stable in platelet-poor plasma (33) and only 40% is extracted during passage through the lungs (34). These observations raise the possibility that endogenous 6KE may play a role in gestational and perinatal events in the fetus.

In all maternal tissues examined, the concentrations of 6KE were significantly lower than those of 6KF. This was also true for all fetal tissues measured except the kidney and liver, where 6KF concentrations were also very low. In addition to platelets (14), 9-hydroxy PG dehydrogenase activity has been found in liver and kidney (35, 36).

These results suggest that 6KF is consistently the major metabolite of PGI_2 in maternal and fetal ovine tissues. Whether endogenous 6KE production has any physiologically relevant role cannot be determined from this study. We have observed, however, that while amniotic fluid, fetal carotid artery plasma, and maternal vena caval plasma (representing uterine effluent) concentrations of all other measured PG increased with the onset of labor in sheep (13), no change occurred in 6KE concentrations in these same animals (37), suggesting that the physiological role of endogenous 6KE may be minimal.

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