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THE METABOLISM OF PROSTAGLANDINS BY THE GUINEA-PIG UTERUS WITH PARTICULAR REFERENCE TO CORPUS LUTEAL MAINTENANCE IN EARLY PREGNANCY

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1 Homogenized lung tissue from day 15, pregnant and non-pregnant guinea-pig metabolized exogenous prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) almost completely when incubated in Tyrode solution containing β-nicotinamide adenine dinucleotide (NAD^+).

2 Metabolism of PGE_2 and $PGF_{2\alpha}$ by homogenates of day 15, pregnant or non-pregnant, guinea-pig uteri was relatively low (8 to 20%) when incubated in Tyrode solution containing NAD^+.

3 Day 15, guinea-pig conceptuses (placentae and embryos), homogenized and incubated in Tyrode solution containing NAD^+, metabolized prostaglandins to a slightly greater extent (14 to 22%) than day 15, uterine tissue.

4 Addition of exogenous arachidonic acid to day 12 or day 15, pregnant, guinea-pig uterine homogenates in Tyrode solution did not increase the yield of $PGF_{2\alpha}$ following incubation.

5 It is concluded that neither an increase in metabolism of $PGF_{2\alpha}$ by the uterus and conceptus nor lack of precursor is responsible for the lower secretion of $PGF_{2\alpha}$ from the day 15, pregnant, guiena-pig uterus when compared to the day 15, non-pregnant uterus.

Introduction

There is now substantial evidence that prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is the uterine luteolysin in the guinea-pig (Poyser, 1976). The non-pregnant, guinea-pig uterus shows a cyclical variation in the amount of $PGF_{2\alpha}$ produced when homogenized and incubated *in vitro*, a large increase being seen around day 15 of the oestrous cycle, associated with luteal regression (Poyser, 1972). In the pregnant guinea-pig however, a functional corpus luteum is maintained beyond day 15 (Heap & Deanesly, 1966) and the amount of $PGF_{2\alpha}$ released from the day 15, pregnant uterus is very much less than that for the day 15, non-pregnant guinea-pig uterus (Blatchley, Maule Walker & Poyser, 1975). The reduction in the amount of $PGF_{2\alpha}$ released from the pregnant uterus is thought possibly to account for luteal maintenance in early pregnancy. The reduced $PGF_{2\alpha}$ release might be achieved either by a rapid breakdown of any $PGF_{2\alpha}$ formed or by an inhibition of synthesis of $PGF_{2\alpha}$ by the uterus. In this paper the metabolism of $PGF_{2\alpha}$ and prostaglandin E_2 (PGE_2) by the day 15, non-pregnant guinea-pig uterus is compared with that of the day 15, pregnant guinea-pig uterus. The possibility that the levels of arachidonic acid, the precursor of $PGF_{2\alpha}$ and PGE_2, may be a limiting factor in the synthesis of prostaglandins by the early pregnant guinea-pig uterus is also investigated.

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Methods

Estimation of oestrous cycle lengths in virgin female guinea-pigs and mating procedures were as described before (Maule Walker & Poyser, 1974). Day 1 of the oestrous cycle was taken to be the day preceding the post-ovulatory leucocytic influx. Day 1 of pregnancy was taken to be the day when spermatozoa were first observed in the vaginal smear.

Metabolic studies

Nine, day 15, non-pregnant and eight, day 15, bilaterally pregnant guinea-pigs were killed by stunning and incising the neck, and the uteri were removed. The uteri of the pregnant animals were freed of any placental and embryonic tissues, these being retained. The uterus from one, day 15, non-pregnant guinea-pig

was weighed, chopped and homogenized in 25 ml chilled incubation medium and then boiled for 10 minutes. The incubating medium used throughout was made up of Tyrode solution (composition g/l: NaCl 8.0, KCL 0.2, $CaCl_2$ 0.2, $MgCl_2$ 0.1, NaH_2PO_4 0.5, $NaHCO_3$ 1.0, glucose 1.0) containing β-nicotinamide adenine dinucleotide (NAD^+, 2.0 mM). The remaining uteri from the non-pregnant and pregnant guinea-pigs were weighed, chopped and homogenized in 25 ml incubation medium by methods previously described (Maule Walker & Poyser, 1974). The placental and embryonic tissues (conceptuses) were treated in the same manner as the uteri. A piece of lung from each of the non-pregnant and pregnant guinea-pigs was similarly weighed, chopped and homogenized in 25 ml incubation medium. All homogenates were divided into two equal parts and kept on ice until the incubation was started. Eight flasks of 12.5 ml incubation medium alone were also set up.

(a) *Determination of total metabolism.* [^{3}H]-$PGF_{2\alpha}$ 0.5 μCi (sp. act. 85 Ci/mmol) and $PGF_{2\alpha}$-tromethamine salt 10 μg in 100 μl incubation medium were added to one part of each of five homogenates of each type (i.e. non-pregnant uterus, pregnant uterus, conceptus and lung from non-pregnant and pregnant animals), to one of the flasks containing incubation medium only and to one part of the boiled uterine homogenate. [^{3}H]-PGE_2 0.5 μCi (sp. act. 160 Ci/mmol) and PGE_2 10 μg in 100 μl incubation medium were added to the other part of each of these homogenates. All the homogenates were incubated at 37°C for 90 min with continuous oxygenation and shaking.

(b) *Determination of rate of metabolism.* [^{3}H]-$PGF_{2\alpha}$ 5 μCi and $PGF_{2\alpha}$-tromethamine salt 10 μg in 100 μl incubation medium were added to one part of the three homogenates of each type remaining, including the flasks of incubation medium alone, which acted as controls against which metabolism was calculated. [^{3}H]-PGE_2 5 μCi and PGE_2 10 μg in 100 μl incubation medium were added to the other part of all the remaining homogenates, including the control, medium alone, flasks. All the flasks contained a final volume of 12.6 ml. All incubations were carried out at 37°C with continuous oxygenation and shaking. A 500 μl aliquot was taken from every homogenate immediately (1 to 5 s) after addition of exogenous prostaglandin, when the incubation was started. Subsequently 500 μl aliquots were removed from every homogenate at 30 s, 1 min, 5 min and thereafter at 5 min intervals for 30 min, then at 60 min and 90 min after the start of incubation.

All samples were acidified to pH 4.0 by the addition of 0.1 N HCl immediately on completion of incubation or removal as an aliquot during incubation. Prostaglandins and their metabolites were extracted by solvents (Poyser, 1972), and, following evaporation, re-dissolved in 100 μl MeOH and subjected to thin-layer chromatography. [^{3}H]-$PGF_{2\alpha}$ and [^{3}H]-PGE_2 were run as radioactive marker standards. Neutral silica gel (200 mm × 200 mm × 0.25 mm) on glass plates was used. Non-radioactive marker standards (10 μg of each of $PGF_{2\alpha}$, PGE_2, 13,14-dihydro-PGE_2, 13,14-dihydro-$PGF_{2\alpha}$, 13,14-dihydro-15-oxo-PGE_2 and 13,14-dihydro-15-oxo-$PGF_{2\alpha}$) were applied to five control plates. A double-run development of all the plates was performed using initially solvent system FVI (Andersen, 1969) and then solvent system GCM (Millar, 1974). The plates were scanned with a Panax radio thin-layer chromatographic plate scanner. The positions of any radioactive bands were identified from the scans and their position relative to the origin and solvent front recorded. The radioactive bands were then each scraped off and washed five times with 3 ml MeOH, the washings combined and taken to dryness. The dry residue was in each case taken up in 0.1 ml MeOH; 50 μl of the dissolved residue was added to 10 ml toluene: ethoxyethanol-based scintillant (Hensby 1974) and counted in a Nuclear Chicago liquid scintillation counter. In the total metabolism studies the percentage of initially added radioactivity retrieved from each radioactive band was calculated. For the rate of metabolism studies, the radioactivity retrieved from each radioactive band for any aliquot was expressed as a percentage of the total radioactivity found for a 500 μl aliquot of 12.5 ml incubation medium containing 5 μCi of tritiated prostaglandin and 10 μg cold prostaglandin. The non-radioactive marker standards were identified by developing the plate by spraying with a saturated solution of phosphomolybic acid in ethanol, and heating at 115°C for 15 minutes. The positions of the spots were recorded relative to the origin and solvent front, and the R_F values were determined.

Arachidonic acid studies

Eighteen bilaterally pregnant guinea-pigs were used. Nine were killed on day 12 and nine on day 15 of pregnancy. The uteri were removed and freed of all embryonic and placental tissue. The uteri were each then weighed, chopped and homogenized in Tyrode solution with a Polytron homogenizer. Three, day 12, pregnant uteri and three, day 15, pregnant uteri were each homogenized in 20 ml Tyrode solution. Three, day 12, pregnant uteri and three, day 15, pregnant uteri were each homogenized in 19.9 ml Tyrode solution and 0.1 ml of ethanol was then added to each. The other three, day 12, pregnant uteri and three, day 15, pregnant uteri were each homogenized in 19 ml Tyrode solution and to each of these was added 1 ml of a solution of arachidonic acid (200 μg/ml) in

Tyrode solution and ethanol, having the ratio Tyrode solution:ethanol of 10:1. All the homogenates were then incubated for 90 min at 37°C with continuous oxygenation and shaking. Homogenates were stored at −20°C before extraction and assay. A 1 ml aliquot of each homogenate was partitioned three times with 3 ml redistilled petroleum ether (b.p. 60 to 80°C), the aqueous phase each time being frozen to allow the petroleum ether to be decanted and discarded. Recovery of [^{3}H]-$PGF_{2\alpha}$ after this partition was 85–87%. Two sets of $PGF_{2\alpha}$ standards were made up in Tyrode solution containing arachidonic acid (10 μg/ml) and 0.1 ml ethanol per 20 ml Tyrode solution and one set was subjected to partition with petroleum ether as described for the homogenates.

Three aliquot volumes were dispensed in duplicate from each homogenate sample that had been partitioned with petroleum ether. The $PGF_{2\alpha}$ content of these aliquots was assayed by radioimmunoassay using solid-phase antibody by methods previously described (Blatchley *et al.*, 1975). The standard curve obtained with the arachidonic acid and ethanol containing standards, with and without petroleum ether partitioning, was compared to that obtained by the normal methods. Quality controls were included in all assays:— a control homogenate (a) was set up in Tyrode solution alone using the uteri from ten, day 7, non-pregnant guinea-pigs. $PGF_{2\alpha}$ was added to an aliquot of this control homogenate (a) at a concentration of 6 ng/ml. The amount of $PGF_{2\alpha}$ in the control homogenate (a) and in the homogenate containing added $PGF_{2\alpha}$ at 6 ng/ml (homogenate b) was determined in every assay, both before and after partitioning with petroleum ether to determine the effect of the partitioning on the recovery of known amounts of $PGF_{2\alpha}$. The effect of the presence of ethanol and arachidonic acid, at the concentrations used for the experimental samples, on the recovery of the known amounts of $PGF_{2\alpha}$ in the control homogenates (a) and (b), using the same method of partitioning with petroleum ether as for the experimental samples was also determined.

The standard error of the mean (s.e. mean) was calculated for all results where possible. Significance of results was determined by Student's *t*-test.

Results

Metabolism studies

The R_F values for the non-radioactive marker standards are shown in Table 1.

Total metabolism. Most of the radioactivity recovered from homogenates of the uterus or conceptus was located at R_F values corresponding to the authentic standards, $PGF_{2\alpha}$ and PGE_2 (Table 2). Where metabolism occurred, the major radioactive metabolite had a R_F value corresponding to the 13,14-dihydro-15-oxo-prostaglandin derivative. From the non-pregnant guinea-pig uterine and lung homogenates a smaller quantity (1 to 4%) of the radioactive material recovered was located at the R_F value corresponding to the 13,14-dihydro-prostaglandin metabolite. In addition 0.5% of the radioactivity recovered from the metabolism of [^{3}H]-$PGF_{2\alpha}$ by the non-pregnant uteri was located at R_F 0.72, and remained unidentified.

The percentage metabolism (Table 3) of added radioactive prostaglandin was calculated for each sample by taking the parent band values for the radioactive marker standards as zero metabolism.

The day 15, guinea-pig conceptuses metabolized prostaglandins to a greater extent then either the non-pregnant or pregnant uteri but metabolism never exceeded 22%.

Rate of metabolism. The percentage metabolism of initially added radioactive prostaglandin was calculated for each aliquot, taking as zero metabolism the mean parent band values for the aliquots taken at the same time from the flasks containing incubation medium and prostaglandins but no tissue. The mean percentage metabolism was plotted against time for each type of tissue incubated (Figure 1). Maximum metabolism of prostaglandins by the lung tissue had occurred within 30 s of addition of exogenous prostaglandin. The other tissue types incubated reached maximum metabolism in 5 to 10 minutes. The rates of metabolism of prostaglandins by the uteri and conceptuses were so low that any mathematical expression of rate would not add significantly to the information given by Figure 1.

Arachidonic acid studies

The standard curve obtained with $PGF_{2\alpha}$ in Tyrode solution:ethanol (19.9:0.1) containing arachidonic acid 10 μg/ml was superimposable on the standard curve obtained using $PGF_{2\alpha}$ in assay diluent after partitioning with petroleum ether. If partitioning with

Table 1 Mean R_F values (±s.e. mean) for non-radioactive marker standards in five control chromatograms

Substance	R_F
Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)	0.33 ± 0.03
Prostaglandin E_2 (PGE_2)	0.51 ± 0.01
13,14-Dihydro-$PGF_{2\alpha}$	0.49 ± 0.01
13,14-Dihydro-PGE_2	0.66 ± 0.02
13,14-Dihydro-15-oxo-$PGF_{2\alpha}$	0.60 ± 0.02
13,14-Dihydro-15-oxo-PGE_2	0.77 ± 0.03

Table 2 Percentage of added radioactivity (mean ± s.e.) recovered from thin-layer chromatography plates at R_F values (see Table 1) associated with prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and their metabolites after 90 min incubation

	Radioactivity recovered (%)					
Radioactive prostaglandin added	[^{3}H]-$PGF_{2\alpha}$ (0.5 μCi)			[^{3}H]-PGE_2 (0.5 μCi)		
Non-radioactive prostaglandin added	$PGF_{2\alpha}$ (10 μg)			PGE_2 (10 μg)		
Mean R_F (±0.02) of radioactive bands	0.32	0.49	0.61	0.51	0.66	0.77
Sample (n = 5 in all cases)						
Standard prostaglandin without incubation, no medium, no tissue	68.7 ±2.9	nd	nd	65.3 ±3.2	nd	0.7 ±0.2
Tyrode + NAD^+ (0.2 mM) no tissue present	65.3	nd	nd	61.2	nd	2.9
Boiled uterus from day 15, non-pregnant guinea-pig	65.1	nd	0.6	60.4	nd	3.2
Day 15, non-pregnant, guinea-pig uterus	60.1 ±1.3	1.8 ±0.4	3.7 ±0.6	54.1 ±1.6	0.7 ±0.2	8.4 ±0.6
Day 15, pregnant, guinea-pig uterus	57.9 ±1.1	nd	7.2 ±0.7	50.3 ±0.9	nd	12.9 ±0.8
Day 15, guinea-pig conceptuses	55.5 ±2.1	nd	9.8 ±1.1	49.8 ±1.7	nd	14.1 ±0.6
Day 15, non-pregnant, guinea-pig lung	0.9 ±0.2	nd	67.2 ±2.9	0.6 ±0.2	2.8 ±0.4	62.9 ±2.5
Day 15, pregnant, guinea-pig lung	0.2 ±0.1	nd	68.6 ±2.1	0.2 ±0.1	1.9 ±0.6	64.2 ±2.6

nd = no detectable radioactivity. All samples incubated in Tyrode solution containing NAD^+ (0.2 mM) except where stated.

petroleum ether was not carried out the standard curve was displaced and flattened at either end. Evidently the partitioning with petroleum ether was essential for the assay to be valid.

The mean value obtained for the quality controls when known amounts of $PGF_{2\alpha}$ (6 ng/ml) were added to uterine homogenates and subjected to petroleum ether partitioning was 5.7 ± 0.6 ng/ml after subtraction of the $PGF_{2\alpha}$ level in the homogenate alone (11.7 ± 0.5 ng/ml). Neither the presence of ethanol nor arachidonic acid, at the concentrations used in this experiment, in the Tyrode solution significantly reduced the recovery of known amounts of $PGF_{2\alpha}$ (6 ng/ml) added to the uterine homogenates. Following petroleum ether partitioning, the mean values obtained for the added $PGF_{2\alpha}$ were 5.4 ± 0.7 ng/ml and 5.5 ± 0.5 ng/ml respectively. These results indicate that the use of radioimmunoassay was valid.

Table 3 Total percentage metabolism of added radioactive prostaglandin by each sample in a 90 min incubation

Sample	[^{3}H]-$PGF_{2\alpha}$	[^{3}H]-PGE_2
Incubation medium alone	<1%	4.4%
Boiled uterus from day 15, non-pregnant guinea-pig	<1%	4.9%
Day 15, non-pregnant, guinea-pig uterus	8.0%	13.9%
Day 15, pregnant, guinea-pig uterus	10.4%	19.8%
Dat 15, guinea-pig conceptuses	14.3%	21.6%
Day 15, non-pregnant, guinea-pig lung	97.8%	96.3%
Day 15, pregnant, guinea-pig lung	99.9%	98.3%

The amounts of $PGF_{2\alpha}$ produced by the homogenized uteri from day 12 and day 15 pregnant guinea-pigs either in Tyrode solution:ethanol (19.9:0.1) alone or with arachidonic acid (10 μg/ml) are shown in Table 4. There was no significant difference between any of the results obtained.

Discussion

The lung tissue from day 15, non-pregnant guinea-pigs metabolized both $PGF_{2\alpha}$ and PGE_2 extensively. This agrees with *in vivo* observations for the guinea-pig (Piper, Vane & Wyllie, 1970) and shows that the incubation system used here was not limiting metabolism. The lung tissue from day 15, pregnant guinea-pigs similarly metabolized both $PGF_{2\alpha}$ and PGE_2 extensively.

The day 15, non-pregnant and pregnant guinea-pig uteri showed only a small ability to metabolize

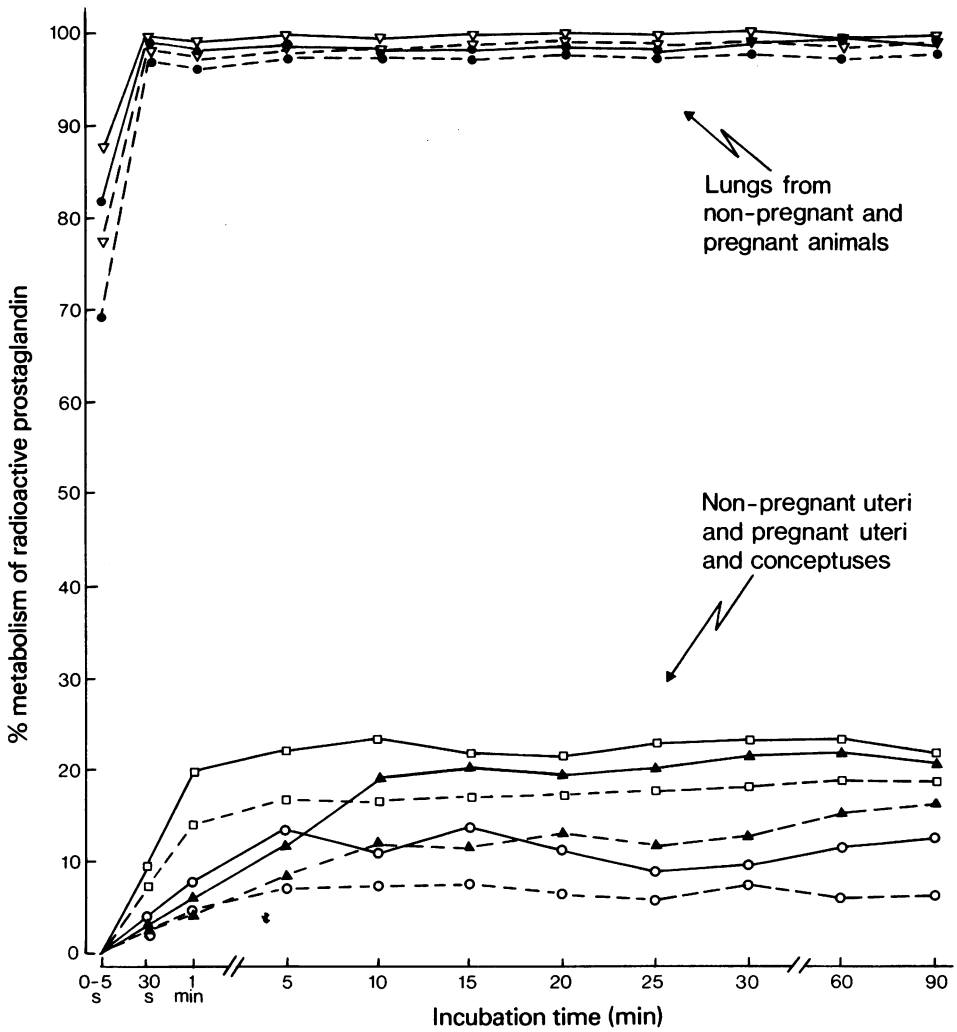

Figure 1 Mean percentage metabolism of radioactive prostaglandin $F_{2\alpha}$ (solid lines) or prostaglandin E_2 (broken lines) after incubation with lung tissue (●) and uteri (○) from day 15, non-pregnant guinea-pigs and lung tissue (▽), uteri (▲) and conceptuses (□) from day 15, pregnant guinea-pigs. For any value s.e. mean was never greater than ±5%.

$PGF_{2\alpha}$ and PGE_2 when incubated in Tyrode solution containing NAD^+, and the extent of metabolism by the non-pregnant uteri was similar to that for the pregnant uteri.

The day 15, pregnant guinea-pig uterus produces and releases very much less $PGF_{2\alpha}$ than the day 15, non-pregnant guinea-pig uterus (Maule Walker & Poyser, 1974; Blatchley *et al.*, 1975). This reduction in early pregnancy is thought to account for the maintenance of a functional corpus luteum beyond day 15. Reduced production could be achieved either by a rapid breakdown of any $PGF_{2\alpha}$ formed or by an inhibition of $PGF_{2\alpha}$ synthesis. The absence of any difference in the metabolic abilities between the day 15, pregnant and non-pregnant guinea-pig uteri indicates that the reduced production and release of $PGF_{2\alpha}$ from the day 15, pregnant guinea-pig uterus cannot be accounted for by increased metabolism. In the system described here the day 15, guinea-pig conceptus showed some ability to metabolize $PGF_{2\alpha}$ and PGE_2 but the degree of activity observed is again insufficient to explain the extent of the reduction in

Table 4 The mean (± s.e. mean) amount of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) produced on incubation by homogenized uteri from day 12 and day 15, bilaterally pregnant guinea-pigs

	$PGF_{2\alpha}$ (ng/100 mg uterine tissue)		
Day of pregnancy	*Tyrode solution alone*	*Tyrode solution: ethanol (19.9:0.1)*	*Tyrode solution: ethanol (19.9:0.1) and arachidonic acid (10 μg/ml)*
12	34.9 ± 7.7	35.1 ± 6.2	31.5 ± 8.6
15	33.1 ± 2.9	35.8 ± 3.8	38.0 ± 2.1

release of $PGF_{2\alpha}$ from the early pregnant guinea-pig uterus.

It appears, therefore, that the reduced production and release of uterine $PGF_{2\alpha}$ seen in the early pregnant guinea-pig is the result of an inhibition of prostaglandin synthesis. Reduction of precursor levels (arachidonic acid) would be one means of achieving this end, in which case provision of excess arachidonic acid should overcome the inhibition of $PGF_{2\alpha}$ synthesis. However, the results presented in this paper show that provision of excess arachidonic acid is without effect on the amount of $PGF_{2\alpha}$ released into the incubate of homogenized, day 15, pregnant, guinea-pig uteri and therefore that the endogenous substrate is not lacking.

Inhibition of prostaglandin synthesis could be occurring at an earlier point in the sequence of events leading to $PGF_{2\alpha}$ production and release. The level of prostaglandin synthetase in the uterus is under the control of oestradiol, as studies on the guinea-pig and rat have indicated (Naylor and Poyser, 1975; Ham, Cirrillo, Zannetti and Kuehl, 1975; Wlodawer, Kindahl and Hamberg, 1976). It has been postulated that the increase in synthesis of $PGF_{2\alpha}$ by the guinea-pig uterus towards the end of the oestrous cycle is due to an increase in the level of prostaglandins synthetase in the uterus, caused by the known increase in output of oestradiol from the ovary which occurs at the same time (see Horton & Poyser, 1976). However, in early pregnancy, this increase in oestradiol output from the ovary does not occur (Blatchley *et al.*, 1975). It would appear from this study, therefore, that prostaglandin synthetase levels remain correspondingly low which would account for the reduced synthesis and release of $PGF_{2\alpha}$ by the early pregnant guinea-pig uterus. However, other methods of inhibiting prostaglandin synthesis by the early pregnant uterus cannot be ruled out.

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References

ANDERSEN, N.H. (1969). Preparative thin-layer and column chromatography of prostaglandins. *J. Lip. Res.*, **10**, 316–319.

BLATCHLEY, F.R., MAULE WALKER, F.M. & POYSER, N.L. (1975). Progesterone, prostaglandin $F_{2\alpha}$ and oestradiol in the utero-ovarian venous plasma of non-pregnant and early, unilaterally pregnant guinea-pigs. *J. Endocr.*, **67**, 225–229.

HAM, E.A., CIRILLO, V.J., ZANETTI, M.E. & KUEHL, F.A.S., JR. (1975). Estrogen-directed synthesis of specific prostaglandins in the uterus. *Proc. Natn Acad. Sci. U.S.A.*, **72**, 420–424.

HEAP, R.B. & DEANESLY, R. (1966). Progesterone in systemic blood and placenta of intact and ovariectomized pregnant guinea-pigs. *J. Endocr.*, **34**, 417–423.

HENSBY, C.N. (1974). Reduction of prostaglandin E_2 to prostaglandin $F_{2\alpha}$ by an enzyme in sheep blood. *Biochim. biophys. Acta*, **348**, 145–154.

HORTON, E.W. & POYSER, N.L. (1976). Uterine luteolytic hormone: A physiological role for prostaglandin $F_{2\alpha}$. *Physiol. Rev.*, **56**, 595–651.

MAULE WALKER, F.M. & POYSER, N.L. (1974). Production of prostaglandins by the early pregnant guinea-pig uterus *in vitro*. *J. Endocr.*, **61**, 265–271.

MILLAR, G.C. (1974). A solvent system for thin layer chromatographic separation of prostaglandins and blood pigment. *Prostaglandins*, **7**, 207–208.

NAYLOR, B & POYSER, N.L. (1975). Effects of oestradiol and progesterone on the *in vitro* production of prostaglandin $F_{2\alpha}$ by the guinea-pig uterus. *Br. J. Pharmac.*, **55**, 229–232.

PIPER, P.J., VANE, J.R. & WYLLIE, J.H. (1970). Inactivation of prostaglandins by the lungs. *Nature*, **225**, 600–604.

POYSER, N.L. (1972). Production of prostaglandins by the guinea-pig uterus. *J. Endocr.*, **54**, 147–159.

POYSER, N.L. (1976). Prostaglandin $F_{2\alpha}$ is the uterine luteo-

lytic hormone in the guinea-pig: The evidence reviewed. *Advances in Prostaglandin and Thromboxane Research.* Vol. 2. ed. Samuelsson B. & Paoletti, R. pp. 633–643. New York: Raven Press.

WLODAWER, P., KINDAHL, H. & HAMBERG, M. (1976). Biosynthesis of prostaglandin $F_{2\alpha}$ from arachidonic acid and prostaglandin endoperoxides in the uterus. *Biochim. biophys. Acta*, **431**, 603–614.

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