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ENHANCED INACTIVATION OF PROSTAGLANDIN E_2 BY THE RABBIT LUNG DURING PREGNANCY OR PROGESTERONE TREATMENT

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1 The inactivation of prostaglandin E_2 by the rabbit lung was estimated *in vivo* by comparing its depressor potency following intravenous and intra-aortic injections, and *in vitro* by measuring the rate of disappearance of smooth muscle stimulating activity when the prostaglandin was incubated with high speed supernatant fractions from lung homogenates.

2 The ability of the lung to inactivate prostaglandin E_2 *in vivo* increased gradually throughout pregnancy, and then decreased rapidly during the three days post-partum.

3 An increased lung inactivation was also seen in pseudopregnant (day 12) rabbits, and in non-pregnant rabbits treated with progesterone for 12 days. A further increase occurred when progesterone treatment was prolonged to 26 days.

4 Treatment with oestradiol monobenzoate or cortisol for 12 days, and deprivation of ovarian hormones for 14-17 days by ovariectomy, were without effect on the lung inactivation of prostaglandin E_2.

5 The *in vitro* experiments revealed a striking increase in the activity of lung prostaglandin metabolizing enzymes during pregnancy.

6 The results are discussed in relation to the hormonal changes occurring during pregnancy, and it is suggested that an enhanced lung inactivation of prostaglandins might have an important protective function at this time.

Introduction

The lungs of several animal species are extremely efficient at removing prostaglandins of the E and F series from the circulation (Ferreira & Vane, 1967; Horton & Jones, 1969). Thus, they reduce the passage of prostaglandins from the venous blood into the arterial circulation, where they would otherwise have marked effects on the cardiovascular system. This protective function might be expected to be particularly important at the time of parturition, when there is evidence that uterine activity is aided by endogenous prostaglandins (Waltman, Tricomi & Palav, 1973; Williams, Sneddon & Harney, 1974). However, in humans, it is clear that the lungs do not inactivate all the prostaglandin presented to them during parturition, because the concentrations of prostaglandins E_2 and $F_{2\alpha}$ in ante-cubital venous blood increase during labour, and the levels fluctuate in parallel with the uterine contractions (Karim, 1968; Hertelendy, Woods & Jaffe, 1973). Thus, it seems that either the inactivating mechanism is swamped by large amounts of prostaglandins in the venous blood, or that changes occur during pregnancy which facilitate the passage of prostaglandins through the lungs unchanged. To obtain information about the metabolism of prostaglandins during pregnancy we have studied the rate of inactivation of prostaglandin E_2 by the lungs of non-pregnant, pregnant and post-parturient rabbits.

A preliminary account of some of these results was given at a meeting of the British Pharmacological Society (Bedwani & Marley, 1974).

Methods

Animals

Mature female Dutch rabbits were used throughout these experiments. Where indicated, pseudopregnancy was induced by an intravenous injection

of human chorionic gonadotrophin (HCG, 75 iu). The day of the injection of HCG or of mating was called day 1.

In vivo *experiments*

The method used to measure the inactivation of prostaglandin E_2 by the rabbit lung *in vivo* was in principle that described by Horton & Jones (1969). The loss of vasodepressor activity following a single passage through the lungs was measured by comparison of the depressor potencies of intravenous and intra-arterial injections of the prostaglandin.

Rabbits were anaesthetized with intravenous pentobarbitone sodium. Blood pressure was recorded from a femoral artery. Intra-arterial injections of prostaglandin E_2 were given through a catheter which had been inserted into the right carotid artery and advanced into the ascending aorta. Intravenous injections were given high into the vena cava through a catheter advanced via the femoral vein. Prostaglandin E_2 was dissolved in 0.9% w/v solution NaCl (saline) and each injection was washed in with 0.4-0.8 ml of the solvent.

Responses to a range of intra-arterial and intravenous doses of standard stock solutions of the prostaglandin were obtained. Two doses which gave clearly defined but submaximal depressor responses, usually $<$ and $>$20 mmHg (1 mmHg = 133 Pa) were selected for each route, the ratio between the doses being the same. Then, a fresh dilution suitable for the intra-arterial injections was prepared from the solution to be used for the intravenous injections. The four doses selected were each given 3 to 5 times, following a Latin square design and a dose cycle of 10 minutes. The dose required to cause a 20 mmHg fall in diastolic blood pressure was measured graphically for each route, and the dose-ratio (i.v. dose/i.a. dose) was calculated. This was taken as a measure of the degree of inactivation of the prostaglandin by the lung.

In vitro *experiments*

The metabolism of prostaglandin E_2 by lung enzymes *in vitro* was investigated by measuring its rate of inactivation on incubation with crude enzyme preparations from non-pregnant and pregnant (day 26) rabbits. Inactivation was measured as loss of smooth muscle stimulating activity, since the lung metabolites of prostaglandin E_2 have little activity on smooth muscle (Piper, Vane & Wyllie, 1970).

Lungs, taken from freshly killed animals, were washed thoroughly and homogenized in ice-cold Bucher medium (K_2HPO_4, 0.072 M; KH_2PO_4, 0.02 M; $MgCl_2$, 3.6 mM; nicotinamide, 0.0276 M) to give a tissue : medium ratio of 1 : 9. The homogenate was centrifuged at 1400 *g* for 3 min, after which the supernatant was centrifuged at 100,000 *g* for 1 hour. A 1 ml aliquot of the final supernatant was diluted to 22 ml with Bucher medium and NAD^+ was added to give a final concentration of 2 mM. This crude enzyme preparation was thus equivalent to a dilution of the tissue of 1 part in 220.

To measure enzyme activity, a 10 ml aliquot of this enzyme preparation was incubated at 30° C and the reaction was started by adding 10 μg of prostaglandin E_2. Aliquots (1 ml) of the reaction mixture were removed at the appropriate times and added to tubes containing 0.1 ml of 1 N HCl, a procedure found to inactivate the enzyme preparation. The prostaglandin E_2 in each aliquot was then extracted with 2 x 3 vol. ethyl acetate, and the extracts were evaporated to dryness at 42° C. The residue was dissolved in water, and assayed on the rat stomach strip (Vane, 1957) against prostaglandin E_2 standards.

The efficiency of this extraction procedure was estimated in each experiment by measuring the amount of prostaglandin E_2 which could be recovered from 1 ml of the enzyme preparation kept at 0° C, immediately after the addition of 1 μg of the prostaglandin. The recovery was 93.7% ± 6.0 (mean ± s.e., $n = 6$) and the results have been corrected accordingly.

Aliquots of the enzyme preparation were also taken for determination of total protein, by the method of Lowry, Rosebrough, Farr & Randall (1951), to see if there was any detectable difference between preparations from the non-pregnant and pregnant rabbits.

Results

In vivo *experiments*

Intra-arterial and intravenous injections of prostaglandin E_2 produced rapid falls in diastolic blood pressure which were maximal after 10-16 s and 16-32 s respectively. Recovery was complete within 4 min in most cases, but after an unusually large fall in blood pressure the recovery was sometimes not complete until 7 minutes. In no case was a fall in blood pressure followed by a pressor response, and therefore there was no evidence that the doses used caused catecholamine release.

The log dose-response curves for the prostaglandin did not show any obvious deviations from linearity, but in the majority of experiments the

curve for the intravenous injections was significantly steeper than that for the intra-arterial injections ($P < 0.05$, Student's t test). Thus, the possibility existed that a part of the fall in blood pressure caused by the intravenous doses was due to an action on sites not immediately available to the intra-arterial doses, for example in the heart or lungs. However, large falls in blood pressure caused by prostaglandin E_2 given intravenously were not accompanied by changes in the heart rate (determined from the blood pressure record at a chart speed of 2.5 mm s^{-1}), and were unaffected by bilateral vagotomy (3 experiments). Thus, the intravenous doses had no direct chronotropic effect, nor did they elicit pulmonary or cardiac depressor reflexes.

Another possibility was that, following the intra-arterial injections, a bolus of prostaglandin E_2 might have passed up the left carotid artery to reach the central nervous system and exert a pressor effect (cf. Carlson & Orö, 1966). However, the slope of the intra-arterial dose-response curve was unaffected by clamping the left carotid artery (2 experiments), showing that this was not the case.

Our finding that the intra-arterial and intravenous dose-response curves were not parallel meant that the potency ratio between the two routes could not be calculated by the standard methods applicable to 'four-point' assays. For this reason, comparisons of potency were made by measuring a dose-ratio at one arbitrary response level (20 mmHg).

Effect of pregnancy and parturition

In eight non-pregnant rabbits, in oestrus or anoestrus, the mean dose (±s.e.) of prostaglandin E_2 required to produce a 20 mmHg fall in diastolic blood pressure was 240 ± 74 ng by the intra-arterial route and 2.51 ± 0.54 μg by the intravenous route. The mean dose-ratio was 14.8 ± 2.6.

In pregnant (day 12) or pseudopregnant (day 12) rabbits, the dose-ratios were significantly higher (25.3 ± 2.4 and 29.0 ± 5.8 respectively, Table 1). By days 22-28 of pregnancy the dose-ratio had risen further to 68.8 ± 3.4. These findings are consistent with there being an increase in the rate of inactivation of prostaglandin E_2 in the lungs during pregnancy and pseudopregnancy.

One of our aims was to measure the inactivation of prostaglandin E_2 in the lung during the process of parturition, which usually occurred on day 32. However, as the process of littering could start at any time on this day and was often over within 30 min, this was impractical. Therefore, experiments were performed on day 32 either before any young were born, or immediately after the full litter had been delivered. In the former group, anaesthesia did not prevent the rabbits from attempting to litter, and while this was occurring the blood pressure showed wide fluctuations which were impossible to distinguish from the depressor responses to the prostaglandin. Thus, in order to carry out the experiments at this stage, it was necessary to delay parturition and hence stabilize the blood pressure. This was

Table 1 Comparison of intravenous and intra-arterial doses of prostaglandin E_2 (PGE_2) causing a 20 mmHg fall in diastolic blood pressure before, during and after pregnancy

Condition	*No. of expts*	*Dose of PGE_2 (mean ± s.e.)* *i.v. (μg)*	*i.a. (ng)*	*Dose-ratio, i.v./i.a.* *(Mean ± s.e.)*	*Significance†*
Non-pregnant	8	2.51 ± 0.54	240 ± 74	14.8 ± 2.6	
Pseudopregnant day 12	7	3.22 ± 0.61	115 ± 17	29.0 ± 5.8	$P < 0.05$
Pregnant					
day 12	5	4.57 ± 0.53	198 ± 49	25.3 ± 2.4	$P < 0.02$
days 22-28	5	11.59 ± 0.81	171 ± 17	68.8 ± 3.4	$P < 0.001$
days 31-32:					
starting to litter*	4	16.33 ± 5.02	198 ± 27	89.9 ± 34.6	$P < 0.01$
immediately after littering	2	13.05 (17.8, 8.3)‡	152 (139, 165)‡	89.2 (128.0, 50.4)‡	
Post-partum					
1 day	5	6.21 ± 1.94	142 ± 27	46.3 ± 11.1	$P < 0.01$
2-3 days	3	3.69 ± 1.14	123 ± 32	29.0 ± 1.8	$P < 0.02$

* Given indomethacin (10 mg, i.v.) to stop parturition. ‡ Individual values.
† Significance, compared with the non-pregnant group by Student's t test.

achieved within 1 h by an intravenous injection of 10 mg indomethacin, a substance known to delay parturition in the rat (Aiken, 1972; Chester, Dukes, Slater & Walpole, 1972) and in primates (Novy, Cook & Manaugh, 1974). Under these conditions, the dose-ratios were not significantly different from those on days 22-28 of pregnancy (Table 1). It is possible, however, that the dose-ratios we measured following indomethacin administration were artificially low since this drug is a weak inhibitor of prostaglandin catabolism (Flower, 1974).

In two rabbits anaesthetized within approximately 1 h of littering, the blood pressure was stable and no indomethacin was given. The dose-ratios were similar to those before littering (Table 1). Thus there was no evidence that the lung inactivation of prostaglandin E_2 changes appreciably at the time of parturition.

During the first three days post-partum, however, the dose-ratio fell quickly (Table 1), in contrast with its comparatively slow rise during pregnancy. The results indicate that the rate at which the dose-ratio falls may depend on the litter size. For example, rabbits on day 1 post-partum could be classified into two groups, three which had a litter of 6-9 young and dose-ratios between 40-75, and two with litters of 3 young and dose-ratios of 19.3 and 27.3. The reason for this is not clear. Suckling a large litter *per se* did not ensure a high dose-ratio since two rabbits were suckling litters of 7 and 9 young on day 3 post-partum and had comparatively low dose-ratios of 29.7 and 31.8.

The high dose-ratios found in the pregnant and post-partum rabbits were due to a diminished sensitivity to prostaglandin E_2 given intravenously. The sensitivity of these rabbits to the intra-arterial injections did not differ significantly from that of the non-pregnant controls (Figure 1).

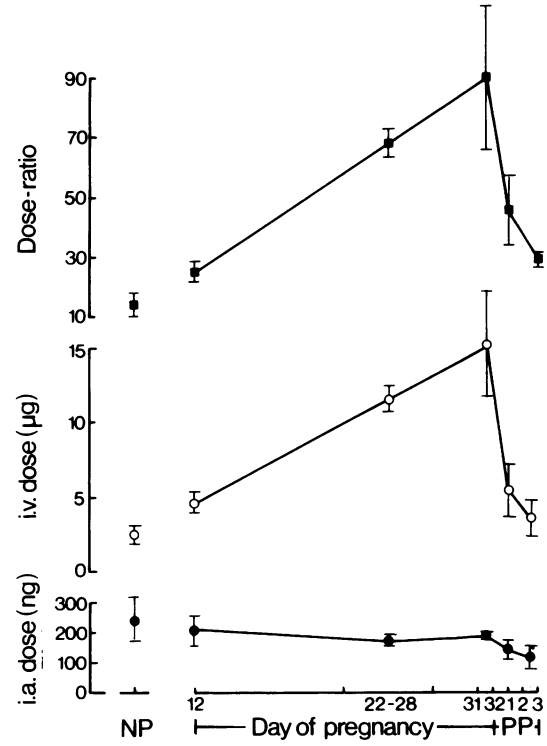

Figure 1 Mean doses (±s.e.) of prostaglandin E_2 required by the intravenous (i.v.) and intra-arterial (i.a.) routes to cause a 20 mmHg fall in diastolic blood pressure in anaesthetized rabbits, either non-pregnant (NP), or on various days of pregnancy or post-partum (PP). The dose-ratio was obtained by dividing the intravenous dose by the intra-arterial dose for each rabbit, and is a measure of the ability of the lung to inactivate prostaglandin E_2. Vertical bars show s.e. mean.

Effect of ovariectomy and of steroid hormones

In three rabbits, ovariectomized 14-17 days before the day of the experiment, the dose-ratios were not significantly different from those in intact non-pregnant controls (Table 2). Thus, this period of deprivation of ovarian hormones had little effect on the inactivation of prostaglandin E_2 by the lung.

Treatment with two hormones, cortisol 25 mg/kg or oestradiol monobenzoate 10 μg/kg, daily for 12 days, had no significant effect on the dose-ratio (Table 2). Treatment with progesterone, 10 mg/kg, or half this dose combined with oestradiol monobenzoate, 5 μg/kg, for 12 days significantly raised the dose-ratio to nearly double that found in rabbits treated with the vehicle (ethyl oleate) alone. These dose-ratios were not dissimilar from those on days 12 of pregnancy and pseudopregnancy. Treatment with progesterone for 26 days raised the dose-ratio almost to the levels found on days 22-28 of pregnancy, although the results were rather variable in the progesterone treated group.

As with the pregnant rabbits, it was the decrease in sensitivity to intravenous prostaglandin E_2 that caused the dose-ratios to be elevated in the progesterone treated rabbits.

In vitro *experiments*

The smooth muscle stimulating activity present in the crude lung enzyme preparations before the addition of any prostaglandin E_2 was equivalent to

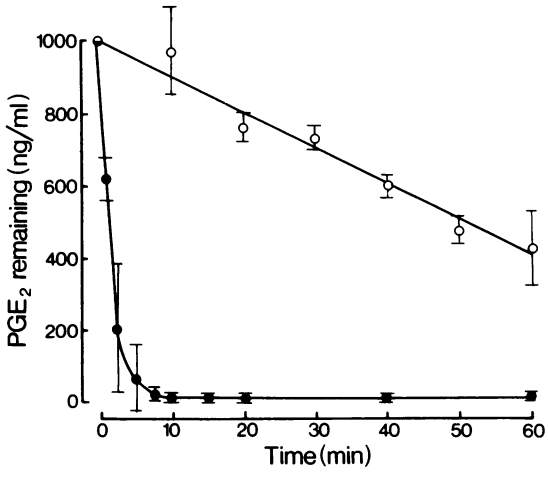

Figure 2 The rate of metabolism of prostaglandin E_2 (PGE_2) in crude enzyme preparations from the lungs of non-pregnant (○) and pregnant (●) rabbits. Each point is the mean value from 3 experiments using enzyme preparations from different rabbits, and refers to the smooth muscle stimulating activity (prostaglandin E_2 equivalents) remaining in the reaction mixture at the times shown. Vertical bars show s.d.

<10 ng prostaglandin E_2/ml in every experiment.

The enzyme preparations from the pregnant rabbits were more potent in inactivating prostaglandin E_2 than those from the non-pregnant rabbits. In the preparations from the pregnant rabbits, the biological activity in the reaction mixture fell from its initial value of 1 μg/ml to 10 ng/ml (prostaglandin E_2 equivalents) in 10-15 minutes. As there was no further loss of biological activity, this residual activity was probably due to the weak biological activity of prostaglandin E_2 metabolites, rather than to unchanged prostaglandin E_2. By contrast, in the preparations from the non-pregnant rabbits, there was still the equivalent of 334-534 ng/ml of prostaglandin E_2 remaining after a 60 min incubation (Figure 2). The half-lives of the prostaglandin in the preparations from pregnant and non-pregnant rabbits were calculated to be approximately 1.5 min and 50 min respectively. The total protein contents of these preparations did not differ significantly, the values being 0.27 ± 0.03 mg/ml and 0.25 ± 0.03 mg/ml respectively (means ± s.e., $n = 3$).

To exclude the possibility that the inactivation of prostaglandin E_2 in the above preparations was caused by blood which had been trapped in the lungs, the stability of the prostaglandin in a 1 in 220 dilution of homogenized blood from pregnant and non-pregnant rabbits was investigated. In neither case was any loss of biological activity detected after incubation for 1 h at 30° C.

Discussion

These experiments show that the capacity of the rabbit lung to inactivate prostaglandin E_2 increases during pregnancy. Most of our evidence was obtained from *in vivo* experiments because we

Table 2 Comparison of intravenous and intra-arterial doses of prostaglandin E_2 (PGE_2) causing a 20 mmHg fall in diastolic blood pressure following ovariectomy or treatment with various steroid hormones

Treatment	*No. of expts*	*Dose of PGE_2 (mean ± s.e.) i.v. (μg)*	*i.a. (ng)*	*Dose-ratio, i.v./i.a. (Mean ± s.e.)*	*Significance†*
Ovariectomy					
14-17 days earlier	3	1.81 ± 0.22	208 ± 84	12.2 ± 4.3	NS
12 days treatment with:					
Ethyl oleate (vehicle)	5	2.76 ± 0.33	152 ± 29	20.1 ± 3.6	
Cortisol 25 mg/kg	3	2.69 ± 0.83	246 ± 115	14.8 ± 7.3	NS
Oestradiol* 10 μg/kg	5	3.37 ± 0.38	152 ± 22	26.2 ± 7.1	NS
Oestradiol* 5 μg/kg with progesterone 5 mg/kg	5	5.10 ± 1.66	149 ± 49	37.5 ± 6.1	$P < 0.05$
Progesterone 10 mg/kg	8	4.60 ± 0.56	142 ± 28	36.7 ± 5.8	$P < 0.05$
26 days treatment with:					
Ethyl oleate (vehicle)	5	1.81 ± 0.29	165 ± 52	13.3 ± 2.7	
Progesterone 10 mg/kg	7	6.61 ± 1.21	121 ± 20	60.6 ± 12.4	$P < 0.02$

* Monobenzoate.

† Significance, compared with ethyl oleate group by Student's *t* test, except for ovariectomized group which was compared with the 'non-pregnant' group (cf. Table 1). NS, not significant ($P > 0.05$).

wished to maintain as closely as possible the conditions existing in the intact animal. For this reason, too, we gave single injections of prostaglandin E_2 rather than infusions because prostaglandin release from the uterus seems to occur in intermittent short bursts rather than as a continuous output (Thorburn, Cox, Currie, Restall & Schneider, 1972).

A difficulty was encountered in that the dose-response curves measured in these experiments were not parallel, those for the intravenous injections being steeper than those for the intra-arterial injections. It is important, therefore, to consider the likelihood of the depressor responses to intravenous prostaglandin E_2 being due, in part, to an action on sites not immediately available to the prostaglandin injected intra-arterially.

We were able to show that intravenous injections of prostaglandin E_2 did not cause changes in heart rate, or evoke depressor reflexes by an action in the heart or lungs. However, another possible way in which the intravenous injections could have caused exaggerated depressor responses is by reducing the cardiac output, and this might have been brought about in several ways. We avoided the possibility of the prostaglandin acting on capacitance vessels, and thereby reducing venous return, by giving the injections high into the inferior vena cava. Another way in which cardiac output can be reduced is by pulmonary vasoconstriction. The occurrence of this in our experiments seems unlikely, as another prostaglandin of the E series, prostaglandin E_1, decreases pulmonary vascular resistance in the rabbit (Hauge, Lunde & Waaler, 1967). However, the effect of prostaglandin E_2 on this parameter does not appear to have been investigated in the rabbit. Finally, the prostaglandin could have had a direct effect on cardiac contractility. Again, this is unlikely as prostaglandin E_2 has little effect on contractile force in the rabbit isolated heart (Hedqvist, Stjärne & Wennmalm, 1970). *In vivo*, prostaglandin E_2 has no direct effect on cardiac contractility in the cat, and increases it in the dog (Jones, Kane & Ungar, 1974).

There was no evidence that our intra-arterial injections of prostaglandin E_2 caused adrenaline release, and we precluded the possibility that the responses to these injections were modified by a bolus of the prostaglandin passing up the left carotid artery to exert a pressor effect via the central nervous system. Thus, the most likely explanation for the steeper dose-response curves for intravenous prostaglandin E_2 is that the lung inactivation mechanism becomes swamped by high prostaglandin concentrations, so that proportionately more escapes metabolism when large doses are given. It is for this reason that we compared the potencies of intravenous and intra-arterial injections at a fairly low response level, i.e. a fall in blood pressure of 20 mmHg.

The results of the *in vitro* experiments showed that the increased inactivation of prostaglandin E_2 during pregnancy can be attributed directly to an increase in the activity of lung metabolizing enzymes, and not to haemodynamic changes which might occur at this time. The correlation between the results of the *in vitro* and the *in vivo* experiments shows that, although the dose-ratio determined *in vivo* was only an arbitrary measurement of lung inactivation, it does appear to be a valid measurement for comparative purposes.

We have made no attempt to identify the lung prostaglandin-metabolizing enzymes operating in our experiments. However, the enzymes most likely to be involved are prostaglandin 15-hydroxy dehydrogenase and Δ13-prostaglandin reductase (Änggård, 1971). It is not possible to determine from the present results whether the increased lung inactivation of prostaglandin E_2 during pregnancy results from an increased affinity of existing enzymes for the substrate or from an increase in the amount of enzyme present. The total protein content of the crude enzyme preparations from pregnant and non-pregnant rabbit lungs did not differ significantly, but clearly such a measurement would be unlikely to detect changes in the concentrations of specific enzymes which presumably constitute only a small fraction of the total lung cytoplasmic protein. It would appear, however, that there is no general increase in the concentration of lung cytoplasmic enzymes during pregnancy.

Recently, Sun & Armour (1974) have studied in detail the levels of prostaglandin 15-hydroxy dehydrogenase and Δ13-prostaglandin reductase in lungs from pregnant and non-pregnant rabbits. They found a 20-fold increase in dehydrogenase and a 3-fold increase in reductase concentrations at days 28-30 of pregnancy compared with those found in non-pregnant rabbits. This provides a biochemical basis for our observation that the lung is able to inactivate prostaglandin E_2 more efficiently during pregnancy.

It was of course of considerable interest to discover the factor responsible for this change in the lungs of pregnant rabbits. It appeared that the plasma concentration of steroid hormones might be of importance since the dose-ratio was found to be increased in pseudopregnant as well as pregnant rabbits on day 12, and we found progesterone treatment to be effective in increasing the lung inactivation of prostaglandin E_2. However, there cannot be a direct relationship between plasma

progesterone levels and lung inactivation, since progesterone levels are at their highest around day 12 of pregnancy and decline subsequently (Challis, Davies & Ryan, 1973a), whereas the lung inactivation shows only a moderate increase at this time, and increases further as pregnancy continues. The possibility that other hormone changes are involved cannot be excluded. For example, the ratio of oestradiol to progesterone increases towards the end of pregnancy (Hilliard, Scaramuzzi, Penardi & Sawyer, 1973), and cortisol levels increase (Mulay, Giannopoulos & Solomon, 1973). However, we found no significant change in lung inactivation when non-pregnant rabbits were treated for 12 days with oestradiol or cortisol.

The slow onset of the increased inactivation during pregnancy compared with its rapid disappearance once the litter was born (Figure 1) is of particular interest. As this slow onset was similar in pregnancy and during progesterone treatment, and since there appears to be no direct correlation between the ability of the lung to inactivate prostaglandin E_2 and the level of progesterone in the plasma, the hormone may increase lung inactivation in an indirect manner. This would reconcile our results with the report that progesterone has an inhibitory effect on placental 15-hydroxy-prostaglandin dehydrogenase *in vitro* (Schlegel, Demers, Hildebrandt-Stark, Behrman & Greep, 1974). Plasma prostaglandin $F_{2\alpha}$ levels in the rabbit show a significant increase between days 21 and 30 of pregnancy (Challis, Davies & Ryan, 1973b), and progesterone has been shown to stimulate uterine prostaglandin $F_{2\alpha}$ production in the sheep (Caldwell, Tillson, Brock & Speroff, 1972; Amoroso, Harrison, Heap & Poyser, 1973). Thus, perhaps an increased level of prostaglandins in venous blood is the stimulus which brings about an increased lung inactivation.

Although we have confined our experiments to the rabbit, there is evidence that a similar effect also occurs in the sheep. Oakes, Mofid, Brinkman & Assali (1973) could not obtain significant changes in blood pressure in pregnant sheep with large amounts of prostaglandin E_2 injected intravenously, and concluded that the sheep is insensitive to prostaglandins, apparently unaware of the findings of Horton, Main & Thompson (1965) that prostaglandins of the E series have marked effects on blood pressure in non-pregnant sheep. Recently, Horton & Maule Walker (personal communication) have shown that the results of Oakes *et al.* (1973) can be explained partially by an enhanced inactivation of prostaglandin E_2 by the sheep lung during pregnancy, and, in addition, have confirmed our observation that this occurs in the rabbit.

Horton & Maule Walker (1975) also attribute some of the insensitivity of the pregnant sheep and rabbit to a decreased sensitivity of the arterial vasculature to prostaglandins. In our experiments, however, the pregnant rabbits were no less sensitive to intra-aortic prostaglandin E_2 than the non-pregnant animals, as is clear from Figure 1.

If an enhanced lung inactivation of prostaglandin E_2 occurs in pregnant women also, then two points need to be considered. Firstly, although intravenous infusions of prostaglandin E_2 are effective in inducing labour (Karim, Hillier, Trussell, Patel & Tamusange, 1970), only a very small proportion of the infused dose would reach the uterus. Thus the human uterus at term might be even more sensitive to prostaglandins than is at present supposed. Secondly, as prostaglandins of the E and F series have been found in the ante-cubital venous blood of women during parturition (Karim, 1968; Hertelendy *et al.*, 1973), assuming that these prostaglandins originate from the uterus, the amounts released into the uterine venous blood must be very large. In such a situation, enhanced lung inactivation would facilitate the removal of prostaglandins from the circulation and could have an important protective function.

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