Effect of Captopril on Uterine Blood Flow and Prostaglandin E Synthesis in the Pregnant Rabbit

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ABSTRACT Captopril, 5 mg/kg, administered to pregnant rabbits caused a reduction in mean arterial pressure (MAP) from 106±2 to 87±2 mmHg ($P < 0.01$) without change in cardiac output or renal blood flow. Uterine blood flow fell from 31.9±2.5 to 21.3±3.4 ml/min ($P < 0.01$) as uterine vein prostaglandin E series level (PGE) decreased from 127±23 ng/ml to 26±8 ng/ml ($P < 0.01$). Saralasin also caused a reduction in MAP from 110±5 to 92±4.3 ($P < 0.01$), a reduction in uterine blood flow from 28.8±1.6 to 21.8±1.7 ml/min ($P < 0.01$) as uterine vein PGE decreased from 121.3±14.4 to 63.5±14.2 ng/ml ($P < 0.01$). Plasma renin activity (PRA) was higher in the uterine vein, 11±3 ng/ml per h, than peripheral vein, 6±1.6 ng/ml per h, ($P < 0.05$), before Captopril and rose in the uterine vein to 90±19 ng/ml per h ($P < 0.01$) as peripheral vein PRA rose to 62±15 ng/ml per h ($P < 0.05$) after Captopril. After saralasin uterine vein PRA rose from 4.6±1.5 to 14.8±6.3 ng/ml per h ($P < 0.05$) and peripheral vein PRA rose from 3.7±1 to 6.5±2.1 ($P < 0.05$).

Reducing MAP with $MgSO_4$ from 98±4 to 70±2 ($P < 0.01$) caused a significant fall in cardiac output from 695±33 to 588±49 ($P < 0.01$) without change in renal or uterine blood flow. Uterine vein PGE concentration also did not change significantly following $MgSO_4$; 80±22 ng/ml before and 60±27 ng/ml (NS) during the administration of $MgSO_4$.

Chronic administration of Captopril in doses of either 2.5 or 5.0 mg/kg per d from the 15th d of gestation caused an 86% fetal mortality at the lower and a 92% fetal mortality at the higher dose of the drug.

These experiments point to the importance of uterine PGE synthesis in maintenance of uterine blood flow and fetal survival during pregnancy and suggest that uterine PGE synthesis is dependent upon angiotensin II. Synthesis of uterine renin and PGE may be necessary for maintenance of uterine blood flow and fetal survival during pregnancy.

INTRODUCTION

During human pregnancy, there is an increase in plasma concentration of renin, angiotensin II (AII),[1] prostaglandin E_2 (PGE_2), and prostacyclin (PGI_2) (1–3). The source of these vasoactive substances is not clear; the elevated plasma renin seems in part of renal origin since in pregnant animals and women, it responds to changes in sodium intake (4, 5). The high plasma PGE_2 is associated with elevated urinary PGE_2 excretion, a reflection of increased renal synthesis (6), so the kidneys may be a source of the elevated plasma PGE_2. However, the uterus of pregnant animals (7) and women (8) contains high concentration of renin and high concentrations of PGE_2 and PGI_2 have been reported in the uterine vein of pregnant animals (2, 9). Whether increased uterine synthesis of these compounds contributes to the elevated plasma concentration seen in human pregnancy is unclear. Renin and PGE_2 may function locally in the uterus as regulators of blood flow; inhibitors of prostaglandin synthesis are known to reduce uterine blood flow in pregnant animals (2) and AII increases uterine blood flow in the pregnant rabbit (10), dog (11), and monkey (12). The increase in uterine blood flow with AII may be caused by uterine prostaglandin synthesis, since AII increases PGE_2 synthesis in the uterus (13), and the increase in uterine blood flow is blocked by indomethacin.

In addition to prostaglandins potentially playing a role in control of uterine blood flow, the increase in plasma PGE_2 and PGI_2 might be the cause of the insensitivity to AII that occurs throughout pregnancy (14). Elevated AII may be required in pregnancy to

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[1] *Abbreviations used in this paper*: AI, AII, angiotensin I and II; MAP, mean arterial pressure; PGE_2, prostaglandin E_2; PRA, plasma renin activity.

overcome antagonism caused by increased synthesis of vasodilating prostaglandins. Saralasin, an angiotensin antagonist, significantly reduces arterial pressure in pregnant rabbits (15), and the decreased AII responsiveness in pregnant women is reversed with indomethacin (16).

To further examine the interrelationship of uterine AII and PGE_2 synthesis during pregnancy, we administered the angiotensin I-converting enzyme, Captopril, acutely and chronically, to pregnant rabbits. Our results demonstrate that uterine synthesis of PGE is dependent on AII and that synthesis of uterine AII and PGE is vital for maintenance of uteroplacental blood flow and fetal survival.

METHODS

Acute studies. Pregnant rabbits were studied on approximately the 26th d of pregnancy. Animals were anesthetized with sodium pentobarbital, 30 mg/kg, and additional doses were administered as necessary to inhibit hindlimb reflexes. The right femoral artery and vein were catheterized (PE 60 tubing) for the purpose of blood pressure monitoring, timed blood withdrawal for blood flow determinations, and the administration of drugs. The left carotid artery was catheterized with PE 190 tubing, which was positioned in the left ventricle. A tracheal catheter (PE 320) was placed for adequate aeration. Through a low, midline incision the uterus was exposed and placed on warm saline soaked gauze. The uterine vein was exposed and dissected free of its fascia. After a sample of blood was obtained from the uterine vein for control measurements of plasma renin activity and PGE_2 concentration, the uterus was returned to the abdominal cavity and the incision clamped shut with small hemostats. 30 min later ~200,000 radioactive microspheres, either 19±2 or 26±2 μm in diam, labeled with either ^{85}strontium or ^{141}cesium, were injected into the left ventricle with simultaneous withdrawal of 2.72 ml/min of blood for 90 s from the femoral artery for measurement or organ blood flow and cardiac output. We have not noted a difference in uterine blood flow when either 19±2- or 26±2-μm microspheres are used. In six pregnant animals the percentage of injected spheres, which lodges in the lungs, was found to be 9.8% after the 19±2-μm microspheres and 8.9% after the 26±2-μm microspheres. Since the injections are made into the left ventricle, we feel the counts in the lung represent the bronchial artery circulation in addition to the small number of microspheres that escape being trapped in the systemic capillaries in both pregnant and nonpregnant rabbits. Following these measurements, Captopril, 5 mg/kg, 20% $MgSO_4$ by constant infusion, or saralasin, (1 sarcosine, 8 alanine, AII), 10 ng/min, was injected intravenously for 45 min through the femoral vein catheter and repeat studies were done. In six animals 1-L-asparaginyl-8-L-valyl AII (Hypertensin-Ciba Pharmaceutical Company, Summit, NJ) was given after Captopril and a third group of measurements were made. In the $MgSO_4$ experiments sufficient dosage of $MgSO_4$ was infused to cause a 20 mmHg fall in mean arterial pressure (MAP).

The animals were killed and the uterus and kidneys removed. The placenta with the underlying attached myometrial tissue was removed from the remainder of the uterine tissue and all tissues were placed in separate vials for digestion of the organ with 18 M HCl to calculate renal, uterine, and placental blood flow. The digestion of the placenta and attached segment of uterus was considered placental blood flow whereas the uterus not underlying placenta was termed uterine blood flow; the combined flows were total uterine blood flow. The digested organ material was then placed in a scintillation vial and counted for the specific isotopes used (gamma 2000, Beckman Instruments, Inc., Fullerton, CA). Organ blood flows were calculated as previously described (17).

Plasma renin activity (PRA) was measured by radioimmunoassay by the method of Haber et al. (18) after incubation for 3 h at ph 5.7. Plasma PGE was measured by immunoassay (19). All samples from one animal were assayed at the same time to avoid interassay variation. The intraassay CV was 4%. The lower limit of sensitivity of this assay is 50 pg/ml. Recovery of [^{3}H]PGE In the experiments was 71±3%. Since the antibody does not differentiate between PGE_1 and PGE_2, we have expressed the results as PGE.

Chronic studies. 33 pregnant rabbits were housed in individual metabolic cages from day 18 of gestation until term. 21 rabbits received Captopril 2.5 mg/kg or 5 mg/kg, s.q. daily while 12 rabbits received only vehicle. On the 29th d of gestation of the animals were killed and the uterus examined for evidence of fetal survival.

Statistics. A paired Student's t test was used to analyze the data within each animal and an unpaired t test was used to analyze the data between groups. In the experiment where AII was administered after Captopril a one-way analysis of variance was used as a test of significance.

RESULTS

Table I demonstrates the hemodynamic data obtained before and after the acute administration of Captopril, 5 mg/kg, i.v., in eight pregnant and six nonpregnant rabbits. MAP fell significantly in the pregnant rabbits ($P < 0.01$) whereas there was no significant change in MAP in the nonpregnant animals. Cardiac output and renal blood flow did not change significantly after Captopril in either group of animals. Total uterine blood flow fell after Captopril, 31.9±2.2 to 21.3±3.4 ml/min, ($P < 0.01$), with placental blood flow falling from 21.2±1.8 to 9.5±1.8 ml/min, ($P < 0.01$), Fig. 1. The fall in total uterine blood flow was entirely due to the fall in placental blood flow since nonplacental uterine blood flow did not change significantly, 10.6±2.2 vs. 11.8±2.5 ml/min.

Saralasin in a dose of 10 mg/min caused MAP to fall from 110±5 to 92±4 mmHg ($P < 0.01$) with total uterine blood flow falling from 28.8±1.6 to 21.8±1.7 ml/min. Placental blood flow fell from 21.7±1.2 to 12.6±1.2 ml/min ($P < 0.01$) during saralasin. Uterine vein PGE concentration fell from 121.3±14.4 to 63.5±14.2 ng/ml ($P < 0.01$) and uterine vein PRA rose from 4.6±1.5 to 74.8±6.3 ng/ml per h ($P < 0.05$) after saralasin. Cardiac output was unchanged 607±43 before and 579±48 ml/min (NS) after saralasin. Similar to Captopril, saralasin did not change renal blood flow 87±9 ml/min before and 85±8 ml/min after saralasin.

When AII was infused after Captopril in sufficient

TABLE I
Hemodynamic Changes with Captopril and $MgSO_4$

	Mean arterial pressure	Cardiac output	Renal blood flow	Total uterine blood flow
	mmHg	*ml/min*	*ml/min*	*ml/min*
Captopril				
Pregnant rabbits (n = 8)				
Before Captopril	106±2	558.3±35.1	80.1±7.3	31.9±2.5
After Captopril	87±2	498.0±46	90.0±10.5	21.3±3.4
	$P < 0.01$	NS	NS	$P < 0.01$
Nonpregnant rabbits (n = 6)				
Before Captopril	105±4	476±57	64±15	
After Captopril	98±5	486±67	58±9	
	NS	NS	NS	
$MgSO_4$				
Pregnant rabbits (n = 9)				
Before $MgSO_4$	98±4	695±33	76±2.7	27±3.8
After $MgSO_4$	70±2	587±49	66±6	23±3.4
	$P < 0.01$	$P < 0.01$	NS	NS

dose to return the arterial blood pressure to at least control values MAP that had fallen from 101±18 to 84±1.6 mmHg ($P < 0.01$) rose to 116.5±1.7 mmHg ($P < 0.01$). Angiotensin caused no change in cardiac output but renal blood flow fell significantly from 83.7±11.9 to 42.5±4.4 ml/min ($P < 0.01$). Uterine blood flow which fell with Captopril from 32.1±3.6 to 29.3±3.6 ml/min ($P < 0.05$) was not significantly changed following angiotensin, 28.2±3.1 ml/min. Placental blood flow that had fallen from 20.8±2.3 to 12.3±1.4 ml/min ($P < 0.01$) after Captopril rose to 15.1±1.8 ml/min with angiotensin and uterine vein PGE that fell from 164±24 to 75.4±15 ng/ml ($P < 0.01$) after Captopril rose to 96.3±17 following angiotensin. These changes in placental blood flow and uterine vein PGE concentration after angiotensin were not statistically significant.

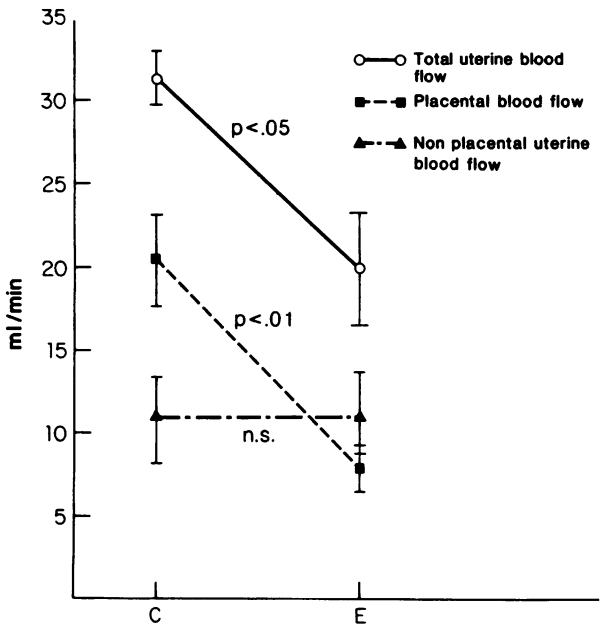

FIGURE 1 Effect of Captopril on uteroplacental blood flow. Uterine and placental blood flow before (C) and 45 min after Captopril administration (E).

$MgSO_4$ caused a fall in MAP from 98±4 to 70±2 mmHg ($P < 0.01$), a significant reduction in cardiac output from 695±33 to 587±49 ml/min ($P < 0.01$) but no significant change in uteroplacental or renal blood flow. Plasma Mg concentration was 8.9±1 meq/liter in these experiments.

Significantly higher PRA was found in the uterine vein than peripheral vein in the control period 11.0±3.0 ng/ml per h compared with 6.0±1.6 ng/ml per h, ($P < 0.05$) and there was a striking increase in uterine vein renin concentration after Captopril to 90.0±19.0 ng/ml per h ($P < 0.01$), with peripheral venous PRA rising to 62.0±19.0 ng/ml per h, ($P < 0.05$). Thus, uterine renin secretion into the circulation occurred before and after AI blockade (Fig. 2).

After Captopril there was a fall in uterine vein PGE concentration from 127±23 ng/ml to 26±8 ng/ml ($P < 0.01$), (Fig. 3). This was not associated with change in peripheral venous PGE that was 1.13±0.06 ng/ml before and 1.12±0.05 ng/ml after Captopril. No significant change in uterine vein PGE occurred with $MgSO_4$; 80±22 ng/ml before and 60±27 ng/ml after $MgSO_4$.

In six other pregnant rabbits renal venous PGE was determined and found to be 3.0±0.3 ng/ml before and

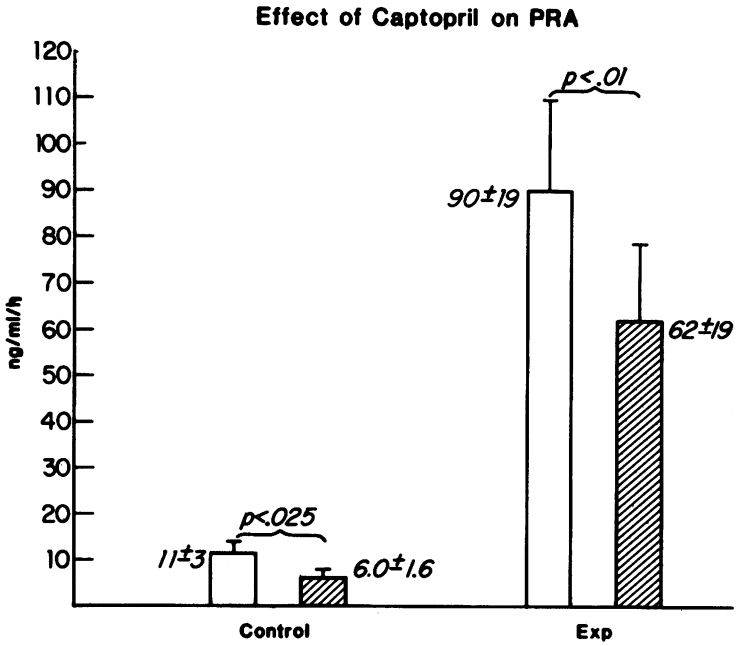

FIGURE 2 PRA in uterine (□) and peripheral vein (▨) before (control) and after (exp.) Captopril.

3.4±0.9 ng/ml after 5 mg/kg Captopril. In five nonpregnant rabbits, the effect of Captopril on urinary PGE excretion was determined. Urine volume was maintained at 1.2 ml/min by intravenous infusion of 5% G/W, and urinary PGE excretion was not altered by Captopril, 7.7±2.8 ng/min before and 12.2±5.7 ng/min (NS) after administration of the drug.

To examine the effect of Captopril on fetal survival, we studied the chronic effect of either 2.5 mg/kg per d (n = 10) or 5.0 mg/kg per d (n = 11) administered subcutaneously beginning on the 18th d of gestation. These results were compared with 12 pregnant rabbits receiving only the vehicle. The results are shown on Table II. The pregnant rabbits receiving only vehicle, had 81 of 82 total fetuses survive, whereas only 24 of the 169 fetuses in pregnant rabbits given Captopril survived until term. With the higher dose of Captopril, 5.0 mg/kg per d, fetal survival was only 7.5%. Blood pressure obtained at the time of killing, approximately the 29th d of gestation, after chronic administration of Captopril, was 115±3 mmHg in the treated animals compared with 108±2 mmHg in animals given only vehicle.

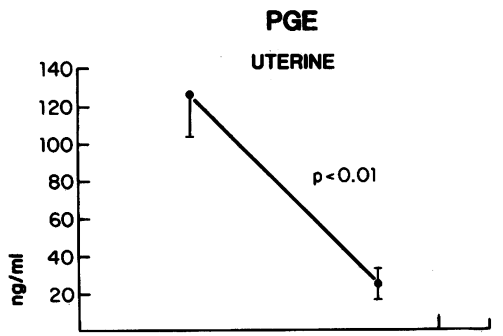

FIGURE 3 Uterine vein PGE concentration before and after Captopril.

DISCUSSION

These studies point to an important physiologic role for uterine AII and PGE synthesis during pregnancy and raise the possibility that control of uterine blood flow depends upon the interdependence of AII and PGE synthesis. Whether the effect of Captopril on

TABLE II
Fetal Survival with Chronic Captopril Administration

	No. of fetuses alive/total	Survival
		%
Controls (n = 12)	80/81	99
Captopril		
2.5 mg/kg (n = 10)	18/89	20
5.0 mg/kg (n = 11)	6/80	7.5

uterine PGE synthesis and uterine blood flow is due to decrease in uterine AII concentration or to some other effect of the converting enzyme inhibitor is difficult to determine. However, the similar effect of saralasin, a competitive inhibitor of AII, in reducing arterial blood pressure, uterine blood flow, and uterine vein PGE concentration makes the effect of Captopril most likely due to blockade of AII synthesis. Converting enzyme inhibitors impair degradation of vasodilating plasma kinins (20), but since bradykinin is known to increase uterine PGE synthesis and blood flow (21) an accumulation of bradykinin is an unlikely cause of the changes seen following Captopril.

The finding that Captopril reduces prostaglandin synthesis has not previously been reported. In contrast, when administered to normotensive subjects, Captopril caused an increase in plasma 13,14-dihydro-15-keto PGE_2, measured by immunoassay, but no change in plasma 6-keto $PGF_1\alpha$ (22). The authors suggested that part of the antihypertensive effect of Captopril might be due to an increase in PGE synthesis, an effect that might be caused by bradykinin accumulation. Our studies demonstrate that at least in the pregnant rabbit, Captopril strikingly reduces uterine PGE synthesis without change in peripheral venous PGE concentration. This lack of effect of Captopril on peripheral PGE suggests that the elevated plasma PGE in pregnancy is not of uterine origin. Since renal synthesis of PGE is increased in pregnancy as indicated by the high urinary PGE excretion in pregnant rabbits (23) and women (5), the elevated plasma PGE might be of renal origin. We found no change in renal venous or urinary PGE excretion following Captopril.

If one roughly compares the secretion rate of uterine and renal PGE, the uterus appears to be a far more significant source of this prostaglandin in the pregnant rabbit. In the control period uterine PGE secretion was ~3,800 ng/min, which fell to 520 ng/min after Captopril. Renal PGE secretion remained ~240 ng/min before and after Captopril. Thus, the failure to demonstrate an effect on plasma PGE after Captopril is difficult to explain. Donker and Venuto (23) found that Captopril increased plasma PGE_2 in nonpregnant rabbits from 0.36±0.21 to 0.92±0.56 ng/ml ($P < 0.01$), whereas it fell in pregnant animals from 1.06±0.23 to 0.81±0.16 ng/ml ($P < 0.025$). Since the uterine circulation contributes such a large quantity of PGE_2 into the circulation in the pregnant rabbit with only modest increase in peripheral PGE_2 concentration the metabolism of PGE_2, particularly in the pulmonary vasculature may increase in pregnancy. Measurements of PGE_2 metabolites would be of interest in pregnancy.

Previous studies have demonstrated that indomethacin reduces uterine blood flow and uterine vein PGE concentration in anesthetized pregnant rabbits (2) and the effect of Captopril reemphasizes the dependency of uterine blood flow on prostaglandin synthesis. The fall in uteroplacental blood flow would appear to be secondary to reduced uterine prostaglandin synthesis rather than reduction in perfusion pressure since $MgSO_4$ failed to reduce uterine blood flow in spite of greater reduction in blood pressure. Previous studies have demonstrated that uterine blood flow in the pregnant rabbit autoregulates flow over a range of mean perfusion pressure from ~60 to 140 mmHg (24).

These studies with Captopril and saralasin also demonstrate that arterial pressure in the pregnant rabbit is dependent upon high levels of circulating AII. Although our studies were done in anaesthetized animals others have reported a similar reduction in pregnant unanaesthetized rabbits following saralasin and Captopril (15) (23). Thus, PGE_2 and AII synthesis during pregnancy may be of importance not only in the control of uteroplacental blood flow but also in maintenance of arterial pressure.

Pregnancy is unlike the nonpregnant state where the concentration of plasma renin and AII can be accounted for on the basis of changes in extracellular volume or sodium balance. Normally, as extracellular volume expands there is an increase in renal perfusion pressure, increased delivery of filtered sodium to the distal tubule and diminished renal sympathetic nerve activity, all of which cause renal renin secretion to fall. During pregnancy, high secretion of renin occurs during expansion of the extracellular volume, increased renal blood flow and glomerular filtration rate and presumably increased delivery of sodium to the macula densa. Persistent secretion of renin and aldosterone occurs in human pregnancy inspite of a high sodium intake (5). This nonsuppressible secretion of renin during volume expansion may be caused by renal prostaglandin synthesis. Prostaglandin synthesis, probably in the juxtaglomerular apparatus, is known to be of importance in control of renin secretion. Cycloxygenase inhibition lowers renal renin secretion and sodium arachidonate, the precursor of prostaglandin synthesis, increases renin secretion both from the kidney and renal cortical slices (25). Pregnancy is similar to Bartter's syndrome where persistent renin secretion occurs during volume expansion. The insensitivity of the vasculature to AII in pregnancy is also similar to Bartter's syndrome where increased plasma PGE_2 and PGI_2 have also been demonstrated (26).

Since blood pressure was not lowered during chronic administration of Captopril, some adaptation must have occurred. We did not measure plasma or urinary PGE during chronic Captopril administration but a reduction in prostaglandin synthesis might decrease the need of high levels of AII to maintain arterial pressure. One problem in interpreting urinary or plasma

PGE_2 concentration with chronic Captopril administration would be determining when fetal death occurred since plasma PGE might fall on that basis. In most of the chronically treated animals we studied, the fetuses were found dead in utero at the time of sacrifice but blood pressure was normal also in animals that had viable fetuses at the time of killing. Thus, we do not feel the failure to see hypotension with chronic Captopril was due to fetal death in all instances.

Conceivably, the component of renin secretion not suppressed by a high salt diet in pregnant women is of uterine origin. High concentration of renin in the uterus of animals and humans has been demonstrated in several studies over the past 20 yr (7, 8) but its potential role in the elevated plasma renin of pregnancy has not been clarified. Uterine renin is released into the circulation during reduction in uterine perfusion (10) or following nephrectomy (7) and in the present experiments uterine venous renin was always higher than peripheral PRA. The increase in uterine renin secretion with Captopril is similar to what occurs in the kidney and suggests that uterine renin release is effected by AII concentration. The uterus may have a "short loop" feedback system where AII inhibits renin release (27) and the uterus, like the kidney, probably possesses the dipeptidyl carboxypeptidase which converts AI to AII. Although this enzyme is located primarily in pulmonary vascular endothelial cells, there is evidence that it exists in all vascular beds (20).

Captopril increases renal blood flow in rabbits when a high plasma renin has been induced by a low salt diet whereas, on a normal sodium intake no increase in renal blood flow or glomerular filtration rate occurs (28). Similarly, in the conscious dog intrarenal infusion of Captopril increases renal blood flow only when the dog is on a low sodium intake (29). It is interesting that activation of the renin angiotensin system with pregnancy is not similar to a low salt intake since no increase in renal blood flow occurs with Captopril or saralasin. The cause of this difference in response is unclear; it is not likely that the renal vasculature is maximally dilated in pregnancy. Increases in renal blood flow occur in pregnant rabbits after hydralazine.[2] It would be interesting to know if Captopril increases renal blood in Bartter's syndrome where the increase in renal secretion is associated with increased prostaglandin synthesis.

With chronic administration of Captopril there was a marked decrease in fetal survival. This is in contrast to other antihypertensive drugs where fetal survival has been improved in hypertensive patients by their use throughout pregnancy (30, 31). Birth weights in women treated with antihypertensive drugs are similar to untreated pregnant hypertensives and there is no evidence of altered fetal growth. The findings we report with Captopril would make it contraindicated in human pregnancy.

It is intriguing to speculate that a possible imbalance in the synthesis of renin and prostaglandin might be a factor in the abnormalities seen in toxemia of pregnancy. The uterine hypoperfusion and the higher fetal mortality present in toxemia, might be due to reduced uterine AII or PGE synthesis. Increased sensitivity to AII occurs with toxemia, which may also reflect a decrease in synthesis of a vasodilating prostaglandin of either uterine or vascular origin. The effect of aspirin, a prostaglandin-inhibiting drug, on pregnancy has been reported in two studies. In one study (32), a high infant mortality and low birth weight was reported, which was not confirmed in another study (33).

In conclusion, uterine blood flow in the pregnant rabbit is dependent upon synthesis of PGE and AII. When AII synthesis is blocked there is a fall in uterine PGE synthesis, a decline in uteroplacental blood flow and a striking rise in fetal mortality. In addition to the effects of AII in controlling uterine blood flow and arterial pressure in pregnancy, fetal survival is also dependent on formation of AII. These findings demonstrate an intimate relationship between uterine production of renin, AII and prostaglandins during pregnancy.

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