Hemodynamic and renal effects of U-46619, a TXA₂/PGH₂ analog, in late-pregnant rats

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1Institute of Pathophysiology, Semmelweis University Medical School, H-1445 Budapest, Hungary; 2Department of Medicine, State University of New York at Buffalo, Buffalo, New York 14215; and 3Department of Physiology, West Virginia University, Morgantown, West Virginia 26505

Kriston, Tünde, Rocco C. Venuto, Christine Baylis, and György Losonczy. Hemodynamic and renal effects of U-46619, a TXA₂/PGH₂ analog, in late-pregnant rats. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R831–R837, 1999.—The vasoconstrictor effects of pressor agents are attenuated during pregnancy. Thromboxane A₂ (TXA₂) is produced in great quantities during hypertension in pregnancy, and therefore it is important to know whether pregnancy modifies the pressor effects of TXA₂. The TXA₂ analog U-46619 was infused in anesthetized, acutely prepared and conscious, chronically prepared late-pregnant and nonpregnant female rats to examine its systemic hemodynamic and renal effects. Mean arterial pressure (MAP) and total peripheral resistance (TPR) were lower in anesthetized pregnant than nonpregnant rats (P < 0.01). The infusion of U-46619 into the aortic arch resulted in elevation of MAP only in pregnant rats, due to a greater elevation of TPR (60 ± 17%) compared with nonpregnant rats (36 ± 6%, P < 0.05). The pressor effect of intravenously infused U-46619 was also enhanced in conscious pregnant versus nonpregnant rats, and the increase in renal vascular resistance was undiminished. U-46619 increased hematocrit and plasma protein concentration more during pregnancy, which suggested greater reduction of plasma volume. The urinary excretion of sodium (~1.49 ± 0.25 vs. ~0.54 ± 0.24 µmol/min) and water was reduced more in pregnant than nonpregnant rats during U-46619 (P < 0.01). Thus the MAP and renal effects of the TXA₂ analog are exaggerated during pregnancy in the rat. pregnancy; thromboxane; renal function

NORMAL PREGNANCY IN WOMEN (1, 28) and in the rat (2) is associated with systemic and renal vasoconstriction diminished hypertensive response to administered ANG II and plasma volume expansion. In preeclampsia these physiological hemodynamic changes are reversed (15, 40), and volume contraction, hypertension, and a reduction in glomerular filtration rate (GFR) ensue. The mechanism of pregnancy-induced vasoconstriction and pressor refractoriness and the reason why these changes are lost in preeclamptic pregnancy remain unknown.

There is evidence (10, 12, 41, 43) for enhanced production of the potent vasoconstrictor thromboxane A₂ (TXA₂) in preeclampsia. An exaggerated pressor action of both U-46619 and IBOP (5-heptenoic acid, 7-(3-[3-hydroxy-4-(4-iodophenoxy)-1-butenyl]-7-oxa-bicyclo[2.2.1]hept-2-yl)-,1S-[1α,2α,(Z),3β(1E,3S,4α)])-, two stable TXA₂/PGH₂ analogs, was observed in late-pregnant versus nonpregnant rabbits (21). That was the first and only in vivo observation of a potentiation of responsiveness to a pressor compound in normal pregnancy. In the present study we compared the systemic hemodynamic effects of U-46619 in nonpregnant and pregnant rats, a species that is more widely used in hypertension research. We also investigated the effects of U-46619 on renal function in conscious, chronically instrumented pregnant and nonpregnant rats.

METHODS

Studies were conducted on 28 female Wistar rats, aged 3–4 mo, obtained from the breeding colony of the Semmelweis University Medical School, Budapest, Hungary, and 14 female Sprague-Dawley rats, aged 3–5 mo, obtained from Harlan Sprague Dawley, Indianapolis, IN. The Sprague-Dawley rats were shipped to the animal care facilities of the West Virginia University Health Sciences Center (Morgantown, WV) at least 7 days before study. All rats were allowed ad libitum access to drinking water and diets containing ~24% protein and 0.5% sodium.

Experiments on anesthetized, acutely prepared Wistar rats (systemic hemodynamics). The effects of U-46619 on cardiac output (CO) and total peripheral resistance (TPR) were studied in anesthetized, acutely prepared, euvolemic Wistar rats bred at Semmelweis University, Budapest. Acute preparation may modulate cardiovascular reactivity, whereas chronic instrumentation for the repeated measurement of CO in the conscious state is technically difficult. We used the acutely prepared model because preliminary experiments (performed on conscious and anesthetized Sprague-Dawley rats at the Department of Physiology, West Virginia University) verified that prior anesthesia and surgery altered neither the pregnancy-induced difference in baseline mean arterial pressure (MAP) and TPR nor the pregnancy-induced changes of the MAP effects of U-46619. Fifteen nonpregnant and thirteen late-pregnant (day 19–20 of pregnancy; term is 22–23 days) rats received intraperitoneal thiobarbiturate (Inactin, 120 mg/kg). Rats were placed on a temperature-controlled table and blood temperature (see below) was maintained at 37.5°C. Euvolemia (volume restoration) (3) was produced by infusion of 5% bovine albumin (Sigma, St. Louis, MO) in sterile isotonic saline initially at 1% body wt/h for 30 min (during surgery), then at 0.15% body wt/h throughout the experiment. Preparatory surgery included a tracheotomy and placement of catheters into the left and right femoral veins (for infusion of plasma and U-46619). A thermistor catheter (PTH-01, Experimetria, Budapest, Hungary) was inserted into the right carotid artery and advanced 3.2 cm from the thyroid cartilage to reach the aortic arch. The right jugular vein was used for the rapid injection of sterile isotonic saline (200 µl) at room temperature and for the measurement of CO by thermodilution, as described earlier (21, 23, 25). MAP and heart rate (HR) were measured through a catheter inserted into the left femoral artery and advanced to the abdominal aorta. After surgical preparation rats were allowed 60 min to
stabilize before experiments were begun. CO was measured, and TPR was calculated by a CO-100 CO computer (Experimetria).

Experiments were as follows. Hemodynamic parameters were recorded in the baseline state on three occasions, 5 min apart, while rats received 5 µl·min⁻¹·100 g⁻¹ iv infusion of isotonic saline. The average of these three readings was considered as baseline. Then, U-46619 (9,11-dideoxy-11a,9a-
epoxymethano-PGF₂α; Cayman Chemicals, Ann Arbor, MI) was infused in doses of 60 and 120 ng·min⁻¹·100 g⁻¹ into eight nonpregnant and seven pregnant rats (intravenously, first experiment). Each dose was infused for 15 min, and hemodynamics were measured at the 5th, 10th, and 15th min. Because the effects of U-46619 reached a plateau within 5 min, typically these three measurements provided similar values, therefore their average was calculated and considered as the representative response. In previously published experiments performed in rabbits (21, 23, 24, 25) we noticed that the route of administration, intra-venous or intra-aortic, substantially influenced the hemodynamic effects of U-46619. Therefore, during a second experiment with other, similarly prepared rats (7 nonpregnant and 6 pregnant), U-46619 (60 and 120 ng·min⁻¹·100 g⁻¹) was administered through the right carotid artery cannula containing the thermistor probe. The experimental design was otherwise similar to the first series of experiments.

Experiments on conscious Sprague-Dawley rats (blood pressure and renal function). Seven nonpregnant and seven pregnant (days 18–21 of pregnancy) rats were chronically catheterized and studied in the awake state. In preliminary surgery conducted under general anesthesia and using sterile technique, Tygon catheters (OD 0.03, ID 0.015 in., Cadillac Plastics, Rochester, NY) were placed in the left femoral artery and vein. Both vascular catheters were forwarded ~1–1.5 in. to end in the abdominal aorta and the vena cava inferior. They were exteriorized at the back of the neck, primed with a 1:1 solution of dextrose (50%) and heparin (1,000 U/ml), and plugged. The bladder was catheterized, irrigated with a neomycin solution, and plugged so that rats were able to void normally through the urethra. This surgery was performed on the 1st day of pregnancy as determined by the presence of sperm in the vaginal smear. Chronic instrumentation did not interfere with normal eating and moving habits and gain of body weight. Pregnancy and fetal development were undisturbed. Further details of this preparation have been reported earlier (4, 33). At least 7 days were allowed for full recovery after surgery. Before experiments, rats were handled extensively and trained to sit quietly in a restraining cage for intervals of 3–4 h.

Experiments on conscious rats were conducted as follows. Rats were placed in a restraining cage, the bladder pin was removed, and a collection tube with a side arm was attached to the catheter. This allows irrigation of the bladder with air (flush volume 0.5 ml) at the beginning the experiment and 2 min before the end of each urine collection, permitting complete recovery of all urine and preventing dead space errors. The indwelling arterial catheter was connected to a pressure transducer, and blood pressure and HR were recorded (ICT-2H Demograph, Gilson, Middleton, WI) via a three-way stopcock to allow continuous recording, except during the time that arterial blood samples were collected. A continuous intravenous infusion of 0.9% NaCl containing tritiated inulin (2–5 µCi/ml) and p-aminohippuric acid (PAH; 1%) was given at the rate of 5 µl·min⁻¹·100 g body wt⁻¹; this is a nonexpanding infusion rate that approximately equals urine output. After an 80-min equilibration period, when plasma inulin and PAH concentrations had plateaued, five consecutive clearance periods of 20-min duration were made. Arterial blood samples (150 µl) were taken at the midpoint of each urine collection. After centrifugation and removal of plasma for later analysis (see below), the red cells were reconstituted with an equal volume of sterile isotonic saline and restored to the rat after the conclusion of the second and the fifth clearance periods. The first two clearance periods provided baseline measurements, and during the 3rd, 4th, and 5th clearance periods, the infusate (inulin and PAH) also contained the the thromboxane A₂ (TXA₂)/PGH₂ analog U-46619 in a quantity to administer 20, 60, and 120 ng·min⁻¹·100 g⁻¹, respectively. Urine collection was started when the elevation of blood pressure plateaued (at the 5th min of infusion).

The volumes of all urine samples were measured gravimetrically and the urine was analyzed for tritiated inulin, PAH, and sodium concentration. Arterial blood samples were analyzed for hematocrit (Hct), plasma protein concentration, tritiated inulin activity, and PAH concentration. Plasma protein concentration was measured on a refractometer. Tritiated inulin activity was measured in 10-µl samples of urine and plasma in a Packard scintillation counter. PAH concentration was measured colorimetrically (36). These measurements allow calculation of inulin clearance, which equals GFR; PAH clearance, which when factored for renal PAH excretion (0.85) reflects renal plasma flow (RPF); and renal vascular resistance (RVR). These calculations are described elsewhere (39).

Statistics. Data are presented as means ± SE. Baseline hemodynamic and renal function data of nonpregnant and pregnant rats were compared by paired t-test. Differences in the effects of U-46619 were analyzed by two-way ANOVA for repeated measures with the post hoc Student-Newman-Keuls test. The frequency of hypotensive episodes during the infusion of U-46619 in conscious nonpregnant and pregnant rats was compared with the χ² test. Differences were considered significant if P < 0.05.

RESULTS

Experiments on anesthetized, acutely prepared rats. The baseline hemodynamic values of anesthetized, acutely prepared rats did not differ between groups receiving U-46619 intravenously or intra-arterially, therefore these parameters were combined and are summarized in Table 1. Pregnant rats were heavier, MAP and TPR were reduced, and HR was moderately increased.

In pregnant rats the infusion of 60 and 120 ng·min⁻¹·100 g⁻¹ iv of U-46619 produced mild increases in MAP (both P < 0.05 vs. baseline; Fig. 1A). In nonpregnant rats, low dose U-46619 slightly increased MAP, but during the infusion of the higher dose MAP tended...

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Wt. g</th>
<th>MAP, mmHg</th>
<th>CO, ml/min</th>
<th>HR, beats/min</th>
<th>TPR, mmHg/ml·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>317 ± 15</td>
<td>111 ± 3</td>
<td>95 ± 4</td>
<td>348 ± 10</td>
<td>1.20 ± 0.07</td>
</tr>
<tr>
<td>P</td>
<td>390 ± 14±</td>
<td>87 ± 4</td>
<td>94 ± 4NS</td>
<td>380 ± 8*</td>
<td>0.84 ± 0.06‡</td>
</tr>
</tbody>
</table>

Values are means ± SE [n = 15 non-pregnant (NP) rats and 13 late-pregnant (P) rats]. MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; TPR, total peripheral resistance; NS, not significant. *P < 0.05, †P < 0.001 vs. NP.
to fall (P < 0.001 vs. pregnant, not significant vs. baseline). In nonpregnant rats CO decreased more during intravenous infusion of U-46619 (P < 0.01) than seen in pregnant rats (Fig 1B). HR did not change in either group (−9 ± 12 beats/min in nonpregnant and 8 ± 7 in pregnant rats, not significant), thus the fall of CO might have been mainly due to a reduction of stroke volume. The elevations in TPR in nonpregnant rats exceeded those of the pregnant rats (P < 0.05 vs. nonpregnant; Fig. 1C).

The route of administration of U-46619 modified its hemodynamic effects in both groups. In pregnant rats intra-aortic administration of U-46619 increased MAP more than after intravenous delivery (P < 0.05), whereas in nonpregnant rats the response to the higher dose was converted from a fall into a slight increase in MAP (P < 0.05 vs. intravenous). During intra-aortic infusion the pressor response was greater in pregnant than nonpregnant rats at each dose (P < 0.001, Fig. 1D), although the fall in CO was similar in the pregnant and nonpregnant groups (Fig. 1E). Thus the larger elevation of MAP in pregnant rats was due to a more substantial relative increase of TPR, by 28 ± 9 and 60 ± 17% compared with 9 ± 4 and 37 ± 6% in nonpregnant rats (P < 0.05). Figure 1F shows that the absolute increase of TPR was also somewhat greater in pregnant rats, but the difference did not reach statistical significance.

At the end of experiments, cesarean section was performed on the pregnant rats. All fetuses were viable, the average litter size was 14 ± 1, and the average pup weight was 2.8 ± 0.5 g (gestational days 19–20).
Experiments on conscious rats. The baseline MAP and renal blood flow (RBF) in conscious, late-pregnant rats were reduced, whereas RVR and GFR were not different versus nonpregnant (Table 2). These measurements confirm earlier reported values of late-pregnant rats (2). Urine flow (V) and urinary sodium excretion (UNaV) were increased, and the gestational plasma volume expansion (2) was reflected by reductions in Hct and plasma protein concentration below the nonpregnant values. The intravenous infusion of increasing doses of U-46619 elevated MAP moderately in both groups (Fig. 2A) and the pressor response was greater in pregnant versus nonpregnant rats at the 120 ng·min⁻¹·100 g⁻¹ dose (P < 0.05). As shown in Fig. 2B, the moderate elevation in MAP with U-46619 was associated with a similar reduction in HR in both groups (from 415 ± 10 to 341 ± 14 beats/min in pregnant rats, P < 0.001; and from 422 ± 11 to 361 ± 13 beats/min in nonpregnant rats, P < 0.001). Furthermore, both groups of rats experienced transient, large falls in MAP during the infusion of 60 and 120 ng·min⁻¹·100 g⁻¹ doses of U-46619. As summarized in Table 3, the magnitude and duration of the hypotensive episodes were similar in pregnant and nonpregnant rats. These events might have exerted minor overall influence on 20-min renal function, because their duration was always shorter than 18 s. When measured, HR was found to be severely reduced (150–250 beats/min). Interestingly, transient episodes of hypotension were never observed in the acutely prepared rats during the infusion of similar doses of U-46619.

In response to this drug, RBF tended to decrease in both groups of conscious rats, but the increase of RVR reached statistical significance only in pregnant rats (both versus baseline and nonpregnant rats; Fig. 2C). The GFR tended to decrease in both groups (Fig. 2D), but the changes did not reach statistical significance. With low dose U-46619 infusion, V and UNaV showed mild increases in both groups, whereas higher doses of U-46619 produced falls in V and UNaV only in pregnant rats (Fig. 3, A and B). The pregnancy-associated potentiation of the antinatriuretic and antidiuretic effects of U-46619 was coupled with enhanced fluid loss from the intravascular space, as reflected by the consistent elevation of Hct and plasma protein concentration (Fig. 3, C and D).

Chronically instrumented pregnant rats delivered spontaneously on the 22nd or 23rd day of pregnancy. Litter size was 13 ± 1, average pup weight was 5.2 ± 0.2 g, all were born alive. This is similar to the reproductive performance seen in untreated rats of the strain.

Table 2. Baseline MAP and renal function in conscious, chronically catheterized NP and P Sprague-Dawley rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Wt, g</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>RBF, ml/min</th>
<th>RVR, mmHg·ml⁻¹·min⁻¹</th>
<th>GFR, ml/min</th>
<th>V, µl/min</th>
<th>UNaV, µmol/min</th>
<th>Hct, %</th>
<th>Ppr, g/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>254 ± 3</td>
<td>119 ± 2</td>
<td>422 ± 11</td>
<td>14.8 ± 1.1</td>
<td>8.3 ± 0.6</td>
<td>2.0 ± 0.1</td>
<td>14.0 ± 2.5</td>
<td>1.73 ± 0.27</td>
<td>43 ± 1</td>
<td>6.3 ± 0.1</td>
</tr>
<tr>
<td>P</td>
<td>348 ± 8†</td>
<td>99 ± 2†</td>
<td>415 ± 10NS</td>
<td>11.8 ± 0.6*</td>
<td>8.7 ± 0.6NS</td>
<td>2.2 ± 0.1NS</td>
<td>26.9 ± 2.6†</td>
<td>2.5 ± 0.3*</td>
<td>35 ± 1†</td>
<td>5.5 ± 0.1*</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 7 NP rats and 7 P rats). RBF, renal blood flow; RVR, renal vascular resistance; GFR, glomerular filtration rate; V, urine flow rate; UNaV, urinary excretion of sodium; Hct, hematocrit; Ppr, plasma protein concentration. *P < 0.05, †P < 0.001 vs. NP.
DISCUSSION

Similar to previous observations made in pregnant rabbits (21), U-46619 increased the systemic hypertensive effect in rats during late pregnancy. This contrasts with the reduced pressor responsiveness to other vasoconstrictors (i.e., ANG II, norepinephrine, and vasopressin; Refs. 1, 2, 28). When pregnant rats were given the TXA2/PGH2 analog, renal salt and water retention, hemoconcentration, increased vascular permeability, and reduced CO also developed. Changes of these parameters were exaggerated by the pregnant state as were the antidiuretic and antinatriuretic effects of U-46619. These data, together with our earlier observations in pregnant rabbits (21, 23, 25) support the hypothesis that TXA2 has the characteristics of a mediator of pregnancy-specific forms of hypertension (24). A shift of eicosanoid formation favoring TXA2 versus the vasodilatory prostacyclin and PGE2 has been reported in adriamycin-treated pregnant rats (34), an animal model that possesses some of the features of preeclampsia. Rats with mild underlying adriamycin nephropathy that become pregnant develop hypertension and proteinuria, and signs abate when the animals are treated with a TXA2 receptor antagonist.

TXA2 is a potent vasoconstrictor, and it can induce platelet aggregation (see Ref. 17), increased vascular permeability, and bronchoconstriction (26), as well. TXA2 may mediate the vasoconstrictor effects of other pressor compounds, including ANG II and endothelin in various sites including the placenta (19). Enhanced endogenous synthesis of TXA2 occurs in asthma (26), primary pulmonary hypertension (6), and sepsis (18). These conditions are associated with high pulmonary vascular resistance, intrapulmonary vascular platelet aggregation, and unchanged or low systemic arterial pressure. Preeclampsia may be the only acute clinical condition in which abundant synthesis of TXA2 is not linked to prominent pulmonary hypertension (12, 27). This dissociation may reflect a unique shift of the major site of action of TXA2 from the pulmonary vasculature and platelets to the systemic vasculature during late pregnancy. This speculation is supported by the dramatic reduction in the pulmonary vascular effects of TXA2 analogs in pregnant rabbits (23).

Endothelin (ET) is also a suspected mediator of hypertension in pregnancy, because plasma levels of ET are elevated in preeclamptic women (38) and because the pressor effects of administered ET are undiminished in pregnant rats (30). ET infusion into conscious pregnant sheep induces most signs of preeclampsia (16), and the potent pressor effects of ET in pregnancy may be related to the capacity of ET to increase the in vivo formation of TXA2 (19).

Table 3. Magnitude and duration of sudden, transient hypotensive episodes during the intravenous infusion of U-46619 in conscious NP and P rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose of U-46619, ng·min⁻¹·100 g⁻¹</th>
<th>Change of MAP, mmHg</th>
<th>Change of MAP, mmHg</th>
<th>Recovery time, s</th>
<th>Recovery time, s</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>(7 rats)</td>
<td>$-57 \pm 4$</td>
<td>$-64 \pm 4$</td>
<td>$7 \pm 1$</td>
<td>$14 \pm 3$</td>
</tr>
<tr>
<td></td>
<td>$(n = 10)^*$</td>
<td>$(n = 14)^*$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>(7 rats)</td>
<td>$-58 \pm 3$</td>
<td>$-69 \pm 3$</td>
<td>$9 \pm 1$</td>
<td>$12 \pm 2$</td>
</tr>
<tr>
<td></td>
<td>$(n = 17)^†$</td>
<td>$(n = 15)^†$</td>
<td></td>
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</tr>
</tbody>
</table>

Values are means ± SE; n = no. of hypotensive episodes during infusion of U-46619 (n was compared between 2 groups by χ²). *Six rats had 1–3 hypotensive episodes, 1 rat had none; †6 rats had 1–7 episodes, 1 rat had none. No values were significantly different between pregnant and nonpregnant rats (compared w/ANOVA).

Fig. 3. Changes of urine flow (V; A), urinary excretion of sodium (UNaV; B), hematocrit (Hct; C), and plasma protein concentration (Ppr; D) in conscious, chronically prepared late-pregnant (n = 7) and nonpregnant (n = 7) Sprague-Dawley rats during intravenous infusion of TXA2/PGH2 analog U-46619. $P < 0.05–0.005$ vs. baseline; *P < 0.05–0.005 vs nonpregnant.
At present we cannot identify the mechanism underlying the in vivo potentiation of the systemic vascular effects of synthetic TXA2 analogs. In in vitro studies Weiner et al. (42) observed a diminished pressor response of the uterus (but not the carotid) artery of pregnant guinea pigs to TXA2 analogs. In the intact organism, however, the direct vasoconstrictor effect of U-46619 and IBOP may be modified by vasodilator products released by platelets (13), such as adenosine diphosphate. These, together with other vasodilators (nitric oxide, prostacyclin) derived from the simultaneously stimulated endothelium could convert a potentially vasoconstrictor stimulus to a vasodilator effect. This hypothetical sequence would be more probable in the nonpregnant state, when platelets are highly sensitive to U-46619 (25). The platelets of pregnant rabbits are refractory to U-46619 (25), and therefore such a platelet-induced vasoconstrictor effect may be absent during pregnancy. This in turn would allow an otherwise weak systemic vasoconstrictor action of TXA2 to become fully manifest in the intact gravid animal. Furthermore, in pregnant rats and rabbits, high plasma ANG II levels (2) may potentiate the effects of U-46619 (19).

Pregnancy also blunts the CO-reducing effects of U-46619 seen after intravenous infusion, and a better-maintained CO will contribute to elevation of MAP. TXA2 may depress cardiac function and CO through mediated by angiotensin II. The intravenous injection of U-46619 causes acute pulmonary hypertension and massive pulmonary platelet entrapment in several species. Thus the relatively preserved CO in pregnant rats and rabbits given U-46619 intravenously may be related to diminished coronary, pulmonary, and/or platelet effects of the TXA2 analogs during gestation.

The infusion of 60 and 120 ng·min⁻¹·100 g⁻¹ U-46619 in both nonpregnant and pregnant conscious rats provoked short-term reversible, but dramatic, declines in MAP. During these episodes the animals often gasped and appeared cyanotic. These signs and the severe bradycardia observed during some of these events may have reflected a sudden reduction of CO with consequent generalized hypoxia. Although the mechanism of paroxysmal hypotension induced by U-46619 is not known by us, it may be specific for the female gender, because other investigators have infused identical doses of U-46619 to male Sprague-Dawley rats and male rats have not evidenced such phenomena (Dr. W. J. Welch, personal communication). Gender is known to influence the expression of TXA2 receptors (29), and, compared with females, males respond with an enhanced systemic (35), but attenuated pulmonary (11) pressor response to intravenous U-46619. Therefore, the relatively weak systemic hypertensive effect together with the risk of cardiovascular collapse in females points to the importance of the presence of female and/or the absence of male steroid hormones behind these sexually dimorphic pharmacological responses. Interestingly, acutely prepared females never evidenced these episodes, which might have been due to the protective effect of prior surgery through the activation of various vasodilatory and antiaggregatory mechanisms (22) that could successfully oppose the culminating effects of U-46619.

**Perspectives**

This study demonstrates that the pregnancy-induced potentiation of the effects of TXA2 is not limited to one species. Therefore, it is possible that TXA2 actions will be similarly modified by pregnancy in women. TXA2 may play a role in the pathophysiology of preeclampsia, because its synthesis is enhanced at sites (10, 41, 43) where low-dose aspirin is ineffective. Preeclampsia may frequently be a hyperinsulinemic and hyperandrogenic state (9, 31, 37), and androgens upregulate vascular and platelet TXA2 receptors and increase vasoconstriction and platelet aggregation (29). Indeed, platelets of preeclamptic patients were reported to have increased numbers of specific TXA2 binding sites (32). Thus the further elucidation of how pregnancy and steroid hormones interact with the vascular and platelet actions of TXA2 seems to be of clinical relevance and may shed light on the pathophysiology of preeclampsia.

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**REFERENCES**

BLOOD PRESSURE AND RENAL EFFECTS OF TXA2 IN PREGNANT RATS


