Autoantibodies to the Angiotensin Type I Receptor in Response to Placental Ischemia and Tumor Necrosis Factor \( \alpha \) in Pregnant Rats

Babbette LaMarca, Gerd Wallukat, Mayte Llinas, Florian Herse, Ralf Dechend, Joey P. Granger

Abstract—Circulating factors, such as agonistic autoantibodies to the angiotensin II type 1 (AT1) receptor (AT1-AAs), and inflammatory cytokines, including tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)), are suggested to be important links between placental ischemia and hypertension in preeclamptic women. The purpose of this study was to determine the role of placental ischemia and TNF-\( \alpha \) in stimulating the AT1-AA and the importance of AT1 receptor activation in mediating hypertension during reductions in uterine perfusion pressure (RUPP) and chronic TNF-\( \alpha \) excess in pregnant rats. Increased mean arterial pressure in RUPP pregnant rats (122±1 mm Hg RUPP versus 101±1 mm Hg normal pregnant [NP]; \( P<0.001 \)) was associated with increased circulating TNF-\( \alpha \) (RUPP 48±13 pg/mL versus N 8±1 pg/mL; \( P<0.05 \)) and AT1-AA (RUPP 15.3±1.6 U versus NP 0.6±0.3 U; \( P<0.001 \)). Moreover, TNF-\( \alpha \)–induced hypertension (97±2 to 112±2 mm Hg; \( P<0.05 \)) in pregnant rats was associated with AT1-AA production (TNF-\( \alpha \) rats 9.2±2.3 U versus NP rats 1.0±0.8 U; \( P<0.05 \)). To determine the importance of AT1 receptor activation in mediating hypertension in RUPP– and TNF-\( \alpha \)–treated rats, we administered an AT1 receptor antagonist to RUPP–, TNF-\( \alpha \)–treated, and NP rats. Blood pressure responses were attenuated in RUPP rats (\( \Delta \) 32 mm Hg versus \( \Delta \) 20 mm Hg, NP; \( P<0.001 \)), as well as in TNF-\( \alpha \)–treated rats (\( \Delta \) 10 mm Hg versus \( \Delta \) 5 mm Hg, NP; \( P<0.05 \)). Collectively, these data indicate that placental ischemia and TNF-\( \alpha \) are important stimuli of AT1-AA, and activation of the AT1 receptor appears to, in part, mediate hypertension produced by RUPP and TNF-\( \alpha \) in pregnant rats. (Hypertension. 2008;52:1168-1172.)

Key Words: pregnancy ■ inflammatory cytokines ■ hypertension ■ AT1 receptor activation ■ autoantibodies

Preeclampsia is estimated to affect 5% to 7% of all pregnancies in the United States.\(^1\)–\(^3\) Despite being one of the leading causes of maternal death and maternal and perinatal morbidity, the mechanisms underlying the pathogenesis of preeclampsia remain unclear. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the disease.\(^3\) The initiating event in preeclampsia is postulated to involve reduced placental perfusion that leads to hypertension by mechanisms not yet elucidated.\(^4\)–\(^8\) Recent studies in preeclamptic women demonstrate increased circulating concentrations of an agonistic autoantibody to the angiotensin II type 1 (AT1) receptor (AT1-AA).\(^9\)–\(^17\) The AT1-AA has been purified, and specificity has been demonstrated by Western blotting, colocalization, and coimmunoprecipitation experiments.\(^9\) Because both reductions in placental perfusion The AT1-AA induces signaling in vascular cells, including activating protein 1, calcineurin, and nuclear factor \( \kappa \)B activation, which are blocked by an AT1 receptor antagonist.\(^11\)–\(^17\) This signaling results in increased reactive oxygen species and sFlt-1 production, both of which have been implicated in preeclampsia.\(^14\)–\(^17\) Although these findings suggest that the AT1-AA may be involved in the pathogenesis of hypertension during preeclampsia, the specific mechanisms that lead to excess production AT1-AA are unknown. Furthermore, the importance of AT1 receptor activation in mediating the increase in blood pressure during preeclampsia remains unclear.

Because both reductions in placental perfusion and increases in circulating levels of the inflammatory cytokine TNF-\( \alpha \) have been implicated in preeclampsia, these 2 factors may serve as potential stimuli for the production of AT1-AA.\(^9\)–\(^14\),\(^17\) performed in 4 groups of rats: We have shown previously that placental ischemia in pregnant rats is associated with significant increases in TNF-\( \alpha \), as well as elevated mean arterial pressure (MAP).\(^18\),\(^19\) Moreover, we have reported that chronic infusion of TNF-\( \alpha \) in pregnant rats also mediates an increase in MAP.\(^19\) Therefore, the purpose of this study was to determine the role of placental ischemia and TNF-\( \alpha \), as an inflammatory mediator released in response to placental ischemia, in stimulating the production of AT1-AA. A second objective in the study was to determine the importance of AT1 receptor activation in mediating the increase in blood pressure responses were attenuated in RUPP rats (\( \Delta \) 32 mm Hg versus \( \Delta \) 20 mm Hg, NP; \( P<0.001 \)), as well as in TNF-\( \alpha \)–treated rats (\( \Delta \) 10 mm Hg versus \( \Delta \) 5 mm Hg, NP; \( P<0.05 \)). Collectively, these data indicate that placental ischemia and TNF-\( \alpha \) are important stimuli of AT1-AA, and activation of the AT1 receptor appears to, in part, mediate hypertension produced by RUPP and TNF-\( \alpha \) in pregnant rats. (Hypertension. 2008;52:1168-1172.)

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pressure during placental ischemia, as well as in response to chronic TNF-excess in pregnant rats.

Methods

All of the studies were performed in timed pregnant Sprague-Dawley rats purchased from Harlan, Inc (Indianapolis, Ind). Animals were housed in a temperature-controlled room (23°C) with a 12:12 light:dark cycle. All of the experimental procedures executed in this study were in accordance with National Institutes of Health guidelines for use and care of animals. All of the protocols were approved by the institutional animal care and use committee at the University of Mississippi Medical Center.

Experimental Design

Effect of Reductions in Uterine Perfusion Pressure on AT1-AA and Arterial Pressure

We have described previously the effects of reductions in uterine perfusion pressure (RUPP) in pregnant rats to induce hypertension during pregnancy; this portion of the experiment was performed to determine whether RUPP is a stimulus for AT1-AA production in pregnant rats. Experiments were performed in the following groups of rats: normal pregnant control (NP; n = 12) and RUPP pregnant rats (n = 12). All of the pregnant rats undergoing surgical procedures were anesthetized with 2% isoflurane (WA Butler Co) delivered by an anesthesia apparatus (Vaporizer for Forane Anesthetic, Ohio Medical Products). Pregnant rats entering the RUPP group underwent the clipping procedure at day 14 of gestation. After a midline incision, the lower abdominal aorta was isolated, and a silver clip (0.203 mm ID) was placed around the aorta above the iliac bifurcation. Branches of both the right and left ovarian arteries were clamped using a silver clip (0.100 mm ID), as described previously.18 Rats were also surgically instrumented with a carotid catheter for subsequent arterial pressure measurement on day 19. At day 19 of gestation, arterial pressure and blood samples were collected for AT1-AA measurements.

Effect of AT1 Receptor Antagonism on MAP in RUPP Rats

To determine a role for activation of the AT1 receptor in mediating hypertension in response to placental ischemia, NP and RUPP rats were treated, by gavage, with an AT1 receptor antagonist. The animals were divided into 4 groups: NP (n = 11), NP treated with the AT1 receptor antagonist losartan (NP + AT1; n = 11), pregnant with chronic RUPP (n = 15), and pregnant with chronic RUPP treated with AT1 antagonist (RUPP + AT1; n = 11). For the AT1 receptor antagonist losartan, 1 mg/kg per day was administered by gavage beginning at day 14 of pregnancy.

Effect of TNF-α on AT1-AA and Arterial Pressure in Pregnant Rats

We have demonstrated previously a role for TNF-α in inducing hypertension during pregnancy.6,19 This portion of the experiment was performed to determine the role of AT1-AA production as a potential mechanism of TNF-α-induced hypertension. Experiments were performed in NP rats divided into 2 groups: NP (n = 12) and chronic TNF-α-infused NP (n = 12). TNF-α (Biosource International) was infused at a rate of 50 ng/d for 5 days (day 14 to 19 gestation) via miniosmotic pumps (model 2002, Alzet Scientific Corporation) into NP rats. These rats were also surgically instrumented with a carotid catheter for subsequent arterial pressure measurement on day 19. At day 19 of gestation, arterial pressure was measured, and a blood sample was collected for AT1-AA measurements.

Effect of AT1 Receptor Antagonism on MAP in Response to TNF-α in Pregnant Rats

To determine the role of AT1 receptor activation in mediating TNF-α-induced hypertension, TNF-α was infused into NP rats treated with losartan in the drinking water. Experiments were performed in 4 groups of rats: NP (n = 5), NP treated orally with the AT1 receptor antagonist losartan (NP + AT1; n = 7), chronic TNF-α-infused NP (n = 12), and chronic TNF-α-infused NP treated orally with the AT1 receptor antagonist losartan (NP + TNF-α + AT1; n = 7).

Measurement of MAP in Chronically Instrumented Conscious Rats

Arterial pressure was determined in all of the groups of rats at day 19 of gestation. Pregnant rats were catheterized on day 18 of gestation under anesthesia using isoflurane (Webster) delivered by an anesthesia apparatus (Vaporizer for Forane Anesthetic, Ohio Medical Products). A catheter of V-3 tubing (SCI) was inserted into the carotid artery for blood pressure monitoring. The catheter was tunneled to the back of the neck and exteriorized after implantation. On day 19 of gestation, pregnant rats were placed in individual restraining cages for arterial pressure measurements. Arterial pressure was monitored with a pressure transducer (Cobe III Transducer CDX Sema) and was recorded continuously for a 2-hour period after 1-hour stabilization.

Determination of Serum TNF-α Levels

A rat TNF-α colorimetric sandwich ELISA (R&D Systems) was used for quantification of serum TNF-α levels between 12.5 and 800.0 pg/mL. This assay displayed a sensitivity level of 5 pg/mL, intra-assay variability of 10.0%, and inter-assay of 5.1%, as defined by the manufacturer.

Determination of AT1-AA

Antibodies were detected by the chronotropic responses to AT1 receptor-mediated stimulation of cultured neonatal rat cardiomyocytes coupled with receptor-specific antagonists, as described previously.9,20 Chronotropic responses were measured and expressed in beats per minute.

Statistical Analysis

All data are expressed as means±SEs. Differences between control and experimental groups were analyzed using ANOVA with Student-Newman-Keuls posthoc test. Data were considered statistically different at P values <0.05. Blood pressure comparisons for multigroup and multifactorial analyses were performed by 2-way ANOVA and by using the Bonferroni posthoc test for comparison between control (untreated with losartan) and experimental groups (losartan treated). The criterion for significant differences of the effect of losartan on blood pressure between groups in the study was P<0.05.

Results

AT1-AA Is Produced in Response to RUPP in Pregnant Rats

Associated with the elevation in arterial pressure in RUPP rats were increases in serum levels of AT1-AA. AT1-AA levels in the RUPP rats were 15.3±0.0 mm Hg (P<0.05; Figure 1). The chronotropic response to the RUPP was abolished by the administration of the AT1 receptor antagonist losartan (0.3±0.5 bpm) and by administration of the 7 amino acid–blocking peptides (1.9±1.2 bpm).

MAP in Response to RUPP in the Presence and Absence of the AT1 Receptor Antagonist in Pregnant Rats

MAP was significantly higher (P<0.001) in RUPP rats (122±1 mm Hg) than in NP rats (101±1 mm Hg; Figure 2). In contrast, MAP of RUPP rats treated with the AT1 receptor antagonist averaged 90±2 mm Hg, whereas pregnant rats treated with AT1 receptor antagonist alone had arterial pressure measurements of 81±1 mm Hg (P<0.001). The result of the multifactorial comparison indicates that the effect of

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losartan on MAP in RUPP rats is significantly greater than in losartan-treated NP rats. Although AT1 receptor blockade has a significant effect on MAP in RUPP rats, the increase in pressure is not completely abolished. This is indicative of the importance of activation by other mechanisms controlling blood pressure in response to RUPP in pregnant rats.

**AT1-AA Is Produced in Response to Chronic TNF-α in Pregnant Rats**

The production of AT1-AA is associated with an increase in MAP in response to TNF-α during pregnancy, as illustrated in Figure 3. AT1-AA production in TNF-α-infused pregnant rats was 9.2±2.3 versus 1.0±0.8 bpm in NP rats. We have reported previously that infusing TNF-α into nonpregnant rats does not increase MAP. Likewise, we report here that TNF-α infusion into nonpregnant rats does not stimulate production of the AT1-AA (1.0±0.8 bpm). The chronotropic response to the TNF-α treatment of pregnant rats was abolished by the administration of losartan (0.9±0.4 bpm) and by administration of the 7 amino acid–blocking peptides (1.2±0.7 bpm).

**MAP in Response to TNF-α in the Presence and Absence of the AT1 Receptor Antagonist in NP Rats**

Chronic infusion of TNF-α into pregnant rats resulted in significant increases in MAP relative to control NP rats. MAP (Figure 4) averaged ~112±2 mm Hg in the chronic TNF-α–infused NP rats compared with that of 97±2 mm Hg in control NP rats (P<0.05). Serum TNF-α levels (Figure 4) averaged ~74±11 pg/mL in the TNF-α–treated pregnant rats at day 19 of pregnancy. This was a significant increase as compared with an average of 22±5 pg/mL in control pregnant rats (P<0.05). In contrast, the MAP of chronic TNF-α–infused NP+AT1 receptor antagonist was 102±2 mm Hg, whereas NP rats+AT1 receptor antagonist alone had arterial pressures of 92±4 mm Hg. The serum level of chronic TNF-α–infused NP rats+AT1 receptor antagonist was 72±18 pg/mL, whereas the TNF-α level in NP+AT1 receptor antagonist alone was 32±6 pg/mL (P<0.05).

**Figure 1.** AT1 autoantibodies in RUPP and NP rats as detected by the chronotropic responses (bpm) to AT1 receptor–mediated stimulation of cultured neonatal rat cardiomyocytes coupled with an AT1 receptor–specific antagonist (losartan) and the 7 amino acid–blocking epitope. *P<0.05 vs NP rats; †P<0.05 vs RUPP. All of the data are expressed as means±SEMs.

**Figure 2.** Changes in MAP in response treatment with an AT1 receptor antagonist in RUPP and NP rats. *P<0.001 vs control NP group. All of the data are expressed as means±SEMs.

**Figure 3.** AT1 autoantibodies in TNF-α–infused pregnant rats and NP rats as detected by the chronotropic responses (bpm) to AT1 receptor–mediated stimulation of cultured neonatal rat cardiomyocytes coupled with an AT1 receptor–specific antagonist (losartan) and the 7 amino acid–blocking epitope. *P<0.05 vs NP rats; †P<0.05 vs TNF-α. All of the data are expressed as means±SEMs.

**Figure 4.** MAP and serum TNF-α levels in response to TNF-α infusion and treatment with an AT1 receptor antagonist in NP rats. *P<0.05 vs control group. Data are expressed as means±SEMs.
Discussion
The data obtained in this study demonstrate that increases in MAP in response to RUPP in pregnant rats were associated with increases in circulating levels of TNF-α and the AT1-AA. In addition, TNF-α-induced hypertension in pregnant rats was associated with increased production of the AT1-AA. Moreover, we found that the blood pressure elevations in response to RUPP in pregnant rats and to chronic infusion of TNF-α in pregnant rats were markedly attenuated by pharmacological antagonism of the AT1 receptor. Collectively, these novel findings indicate that placental ischemia and TNF-α are important stimuli of AT1-AA during pregnancy and that activation of the AT1 receptor appears to, in part, contribute to the hypertension produced by placental ischemia and TNF-α in pregnant rats.

Wallukat et al.9 reported previously that sera from preeclamptic women contain an IgG autoantibody that reacts with the AT1 receptor. They used a bioassay for AT1-AA that consists of spontaneously beating neonatal rat cardiomyocytes. The investigators showed that AT1-AA increases the spontaneous beating rate of the cultured cardiomyocytes, an effect that is blocked by AT1 receptor antagonists but not angiotensin II type 2 receptor antagonists or antagonists of adrenergic receptors. They also demonstrated that the AT1-AA binds to a 7–amino acid sequence present on the second extracellular loop of the AT1 receptor. Thus, the findings of Wallukat et al.9 were the first to show that preeclamptic women develop stimulatory autoantibodies against the AT1 receptor and that these autoantibodies are directed to a common epitope associated with the second extracellular loop. Using the bioassay for AT1-AA described by Wallukat et al.,9 we determined the effect of RUPP in pregnant rats on AT1-AA production. The hypertension in the RUPP rats was associated with the AT1-AA. In contrast, the AT1-AA was not detected in NP rats. These novel findings suggest that a reduction in placental perfusion may be an important stimulus for AT1-AA production in preeclampsia.

It is possible that the AT1-AA production in response to RUPP may be secondary to abnormal placental development. A recent report supporting this hypothesis illustrates that the AT1-AA was associated with pregnant women who display abnormal uterine perfusion, as detected by Doppler sonography.13 Using the cardiomyocyte contraction assay, Walther et al.13 found that the AT1-AA was detectable between 18 and 22 weeks in women with abnormal uterine perfusion. These women, when followed to term, fell into 3 groups: those who developed preeclampsia, those characterized by fetuses with intrauterine growth retardation, and those with otherwise normal outcomes. AT1-AA was not observed in second-trimester women with normal Doppler. At term, the AT autoantibody was present in women with preeclampsia, those with intrauterine growth retardation, and even in healthy pregnant women at term with a history of abnormal uterine perfusion in the second trimester.13 Although these findings indicate that reduced uterine perfusion may be an important stimulus for AT1-AA production, the fact that the AT1-AAs are present in patients with pathological uterine artery Doppler, independent of preeclampsia, has led some investigators to suggest that AT1-AA may not be the primary cause of hypertension in preeclamptic women.

It is possible that the generation of AT1-AA in response to RUPP is secondary to the increased maternal inflammatory response that is associated with placental ischemia in pregnant rats. We recently reported that serum levels of TNF-α are elevated in RUPP rats, and chronic infusion of TNF-α into pregnant rats increases arterial pressure and decreases renal plasma flow and glomerular filtration rate.19 In the present study, we not only confirmed that chronic infusion of TNF-α into pregnant rats increases arterial pressure but also provides novel data demonstrating that the hypertension associated with TNF-α infusion in pregnant rats is also associated with the AT1-AA. Although the exact mechanism whereby TNF-α stimulates the production of AT1-AA is not defined, TNF-α is the major stimulus for the activation of macrophages, dendritic cells, and T lymphocytes of the T-helper 1 subset, the predominant cell types mediating the inflammatory cascade in women with preeclampsia.10 Furthermore, macrophages and dendritic cells are antigen-presenting cells for T-helper 1 cells which, in part, aid B lymphocytes in their routine function of immunoglobulin production. In addition, TNF-α mediates the subsequent release of other inflammatory cytokines, such as interleukin 6, which is a major stimulus for B-cell proliferation. It is interesting to note that infusion of TNF-α into nonpregnant rats does not increase blood pressure or the production of AT1-AA. Thus, the ability for TNF-α to stimulate AT1-AA production appears to be a pregnancy specific effect, indicating that the antigen to which the antibody is produced may be more predominately expressed not only in pregnant rats but also in pregnant women during early stages of abnormal placentation.

Although the AT1-AA is elevated in preeclamptic women, pregnant RUPP rats, and pregnant rats with chronic elevations in circulating TNF-α, the importance of AT1 receptor activation in causing hypertension in preeclamptic women or in response to placental ischemia has yet to be fully elucidated. Interestingly, the AT1-AA appears to be responsible for a variety of effects in several different tissues, including increased intracellular Ca++ mobilization, monocyte activation, stimulation of interleukin 6 production, and enhanced production of reactive oxygen species, effects, most of which have been characterized in the RUPP hypertensive rats.9–19 Despite the actions of AT1 receptor activation, the contribution of the activated receptor to the hypertension produced by RUPP in pregnant rats has not been investigated previously. Therefore, a second major objective in this study was to determine the importance of AT1 receptor activation in mediating the increase in blood pressure during placental, as well as in response to chronic TNF-α excess in pregnant rats. We report in this study that treatment with a selective AT1 receptor antagonist, losartan, markedly attenuated the hypertension produced during placental ischemia. Losartan blunted the hypertensive response to TNF-α in pregnant rats; however, this effect was not as profound as the effect of losartan on RUPP rats. These data suggest that activation of the AT1 receptor plays a more important role in...
mediating hypertension in response to placental ischemia than in response to TNF-α in NP rats.

Although our findings indicate that AT1 receptor activation, in part, contributes to the increase in blood pressure in RUPP rats, our results do not quantify the relative importance of the AT1-AA and endogenously formed angiotensin II in activating the AT1 receptor. However, it is important to note that a previous study from our laboratory indicated that chronic inhibition of endogenous angiotensin II formation, via oral administration of a converting enzyme inhibitor, had no effect on the increase in blood pressure in response to placental ischemia. Blood pressure in the untreated RUPP rats was, on average, ≈26 mm Hg higher than the untreated NP rats. Likewise, blood pressure in the converting enzyme inhibitor–treated RUPP rats was ≈25 mm Hg higher than in the converting enzyme inhibitor–treated NP rats. In contrast, our losartan data indicate that blockade of the AT1 receptor does significantly attenuate the BP response to placental ischemia. Blood pressure in the untreated RUPP rats was ≈21 mm Hg higher than in the untreated NP rats. In sharp contrast, blood pressure in the losartan–treated RUPP rats was only ≈9 mm Hg higher than in the losartan–treated NP rats. Although these findings suggest that factors other than endogenous angiotensin II, such as the AT1-AA, may be activating the AT1 receptor in the RUPP hypertensive model, the contribution of AT1-AA in the pathophysiology of hypertension in response to placental ischemia or preeclampsia remains an important area of investigation.

Perspectives

Although the findings of the current study implicate the AT1-AA in mediating hypertension in RUPP– and TNF-α–induced hypertensive pregnant rats, they do not quantify the importance of the autoantibody to mediate hypertension during preeclampsia. Studies inhibiting the generation of the AT1-AA in rats with placental ischemia are necessary to further define the pathophysiological role of the autoantibody to mediate hypertension and renal dysfunction during pregnancy. Finally, specific mechanisms leading to the production of the autoantibody in response to placental ischemia remains an important area of investigation. A better understanding of the pathophysiology of AT1-AA production in preeclampsia may lead to novel therapeutic targets for the treatment of the disease and/or a marker for predicting the risk of developing preeclampsia.

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