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Role of the AT2 receptor in modulating the angiotensin-II contractile response of the uterine artery at mid gestation

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Abstract

Introduction

During human pregnancy, circulating concentrations of components of the renin angiotensin system increase, but pressor refractoriness to angiotensin-II (Ang-II) is observed. Given the importance of the Ang-II pressor response in deciding susceptibility to preeclampsia and of the Ang-II system for controlling uterine vasoreactivity, we sought to address the effects of pregnancy on the reactivity of the isolated uterine artery (UA) in

mice.

Materials and Methods

Blood pressure was measured throughout pregnancy in awake C57BL/6J mice. UA segments were isolated from 3 groups of animals (nonpregnant, mid [day 12–13] and late [day 18–19] gestation) and studied by wire myography.

Results

UA diameters, KCl-mediated responses, as well as acetylcholine-dependent vasorelaxation were greater at mid and late gestation than in non-pregnant animals. Ang-II responses were also greater during pregnancy, with an increased contraction in response to AT2 receptor blockade at mid gestation. AT1 receptor blockade abolished the Ang-II response in all groups.

Conclusions

Study findings are consistent with the possibility that AT2 receptor-mediated vasodilatation plays a role in modulating Ang-II contractile responses in pregnancy.

Keywords: nitric oxide, angiotensin-II, AT2, pregnancy

INTRODUCTION

The uterine artery (UA) and uterine circulation in general make major contributions to the decline in systemic vascular resistance (SVR) during pregnancy (1). In human pregnancy at term, total uteroplacental flow increases approximately 50-fold representing nearly 20% of the cardiac output (CO) (2–4). As part of the maternal cardiovascular responses to pregnancy, the UA undergoes pronounced vasodilatation, growth and remodeling in all species studied to date. Integral to these changes are the UA's increased vasodilator response to flow and pharmacological agonists, greater DNA production, increased proliferative response of UA vascular smooth muscle cells, increased force-generating capacity of the UA smooth muscle, outward hypertrophic remodeling and consequent enlargement in luminal diameter (2;5–8).

The renin angiotensin system (RAS) affects both vasoactive and vascular growth and remodeling-related processes in the systemic as well as the uteroplacental circulations. One of its most important components is the octapeptide angiotensin-II (Ang-II) whose actions are mediated by type 1 (AT1) and type 2 (AT2) membrane receptors. The use of nonpeptide blockers (9) has shown that most

of Ang-II's vasoconstrictor effects are mediated by the AT1 receptor (10) whereas the AT2 receptor has been shown to oppose AT1's effects by causing vasodilatation and natriuresis in several animal models and human studies (11–13).

Several observations point to an important role for the RAS during pregnancy in both the systemic and uteroplacental circulations. In humans, plasma levels of Ang-II and other components of the RAS are increased; however, the systemic pressor response to Ang-II is reduced (14;15). The absence of a blunted pressor response to Ang-II is among the few predictors of susceptibility for preeclampsia (15;16) underscoring the importance of the RAS in this still poorly-understood disease. In sheep, Ang-II vasoconstricts the uterine circulation, but the uterine compared to the systemic vascular bed is relatively refractory to Ang-II. One reason for this may be that pregnancy increases UA AT2 receptor density (17) above its already-elevated levels in the uterine circulation, where it comprises the majority of total Ang-II receptors (18;19). In addition to opposing AT1-mediated vasoconstriction, AT2 receptor activation also stimulates NO production (20). Increased production of NO and other endothelial substances, such as prostacyclin or endothelium-derived hyperpolarizing factor, play important roles in increasing the vasodilator responses of the UA and other systemic vessels during pregnancy (21–23). Given that pregnancy increases AT2-dependent vasodilatation in isolated rat aortae (24) and treatment with an AT2 blocker abolishes the normal mid-pregnancy associated fall in systemic blood pressure in mice (25) and this fall in blood pressure is absent in mice lacking the expression of the Ang-II AT2 receptor (26), we considered that AT2-mediated vasodilatation might also be an important contributor to the pregnancy-associated increase in vasodilator response.

Recently the mouse has emerged as an important model for studying maternal physiological responses to pregnancy since the availability of genetically-modified strains provides unique opportunities for identifying the genes and their mode of action on relevant cardiovascular systems (27). Similar to humans, pregnancy in the mouse decreases vascular resistance, raises cardiac output, lowers blood pressure as well as the pressor response to Ang-II (28;29), and directs much of the increase in flow to the uteroplacental circulation (5). To establish the role of Ang-II receptors in modulating vascular changes during pregnancy and, specifically, the role of the AT2 receptor in opposing AT1-mediated vasoconstriction (25;30;31) (32), we studied the blood pressure response to pregnancy and the effects of Ang-II as well as

other agonists on UA vasoreactivity in the mouse. We hypothesized that enhanced AT2-mediated signaling augmented UA vasodilatation, with such augmentation being particularly evident at mid-pregnancy or the time of greatest fall in systemic blood pressure. To test this hypothesis we measured blood pressure before and then throughout gestation in C57BL/6J mice and used wire myography to compare the contractile and relaxation responses of isolated uterine vessels in nonpregnant, mid (day 12–13) and late (day 18–19) pregnant animals.

MATERIALS AND METHODS

Animals

All procedures were approved by the Wake Forest University School of Medicine Institutional Animal Care and Use Committee. Female and male C57BL/6J mice were obtained from Charles River Laboratories Inc, Wilmington, Mass. Mice were housed in polypropylene cages in a temperature and humidity-controlled environment. Animal housing facilities were controlled on a 12-hour light, 12-hour dark cycle and mice were given free access to standard laboratory chow and water. Non-pregnant (NP) female mice were used between 8–12 wk of age. Mature cycling female mice (7–8 wk old) were used for breeding purposes and studied 2–3 weeks later; the presence of a vaginal plug was taken as indication of Day 0 of pregnancy.

Blood pressure and heart rate measurements

All mice were trained to become familiar with the computerized programmed tail-cuff blood pressure analysis system (Visitech Systems Inc, Apex, NC) before the data were collected, as previously described (25). All data were collected between 8:00 and 10:00 AM. This system permits measuring systolic blood pressure (SBP) and heart rate (HR) in each animal from, on average, 30 values. In non-pregnant animals SBP and HR were recorded during 4 consecutive days. After breeding, SBP and HR were recorded daily throughout pregnancy. SBP and HR for middle gestation (MG) were determined as the average of those measurements obtained at day 12 and 13 of pregnancy while the values for the late gestation (LG) group were determined as the average of the day 18 and 19 values.

Arterial segment preparation

Female NP mice, at MG or LG were killed by cervical dislocation, the uterine horn was removed by laparotomy and the tissue placed

directly into ice-cold Krebs buffer. Under a dissecting microscope the main uterine artery (UA) was identified and dissected free from fat and connective tissue. Uterine vessels from NP (90 μ m), MG (120 μ m) and LG (150 μ m) animals were cut into 1.5–2 mm segments and mounted between an isometric force transducer (Kistler Morce DSC 6, Seattle, WA) and a displacement device on a myograph (Multi Myograph, Model 610M Danish Myo Technologies, Aarhus, Denmark) using two stainless steel wires (diameter 25 μ m). The myograph organ bath (5 mL) was filled with Krebs buffer maintained at 37°C and aerated with 95% O₂–5% CO₂. The vessels were washed and incubated for 30 min before performing the normalization procedure as described (33). Each arterial segment was stretched in a stepwise manner and the internal circumference and corresponding wall tension at each stretch were calculated and plotted to produce a resting wall tension-internal circumference curve for that particular artery using the Myodaq software (National Instruments Corporation, Denmark). Uterine segments were normalized to 0.9 of L_{13.3kPa} as described (33). After obtaining the optimal diameter, a 30-min equilibration period preceded the addition of test substances.

Response to depolarizing concentrations of KCl

In order to test the viability of the arterial preparations and determine responses to non-receptor mediated contraction, segments of UA were exposed successively to increasing concentrations of potassium chloride (KCl). Arterial segments were exposed to eight different concentrations of KCl (6.25–62.5 mM) with each dose maintained for 2 min and the segment washed with Krebs buffer before the subsequent concentration introduced.

Response to U46619

To test the response to a receptor-mediated contraction, arterial segments were exposed to a cumulative concentration-response curve of the thromboxane analog [U41669](#) by exposing arteries to eight (10⁻⁹–10^{-6.75} M) increasing concentrations with each subsequent dose being introduced after a steady response had been reached.

Response to angiotensin-II

In order to avoid tachyphylaxis and desensitization Ang-II was used only once in each arterial segment. Ang-II was administered 30 min after the last contraction of the KCl curve had been relaxed with Krebs buffer, the segments washed 3 times, and Ang II

response was tested as the maximal response to a single 10^{-5} M dose. Since the shape of the Ang-II contraction is such that there is an initial spike and then decline (as shown in [Figure 5A](#)), we elected to measure the contraction at the spike as this represented the point of maximal force generation. In parallel experiments, different arterial segments were preincubated for 15 min with the AT1 receptor inhibitor losartan at 10^{-5} M or the AT2 receptor inhibitor PD-123319 at 10^{-5} M. The Ang-II receptor antagonists produced different effects on Ang-II contraction; losartan 10^{-5} M blocked most of the response whereas PD-123319 at the same dose of 10^{-5} M increased the response in the MG group.

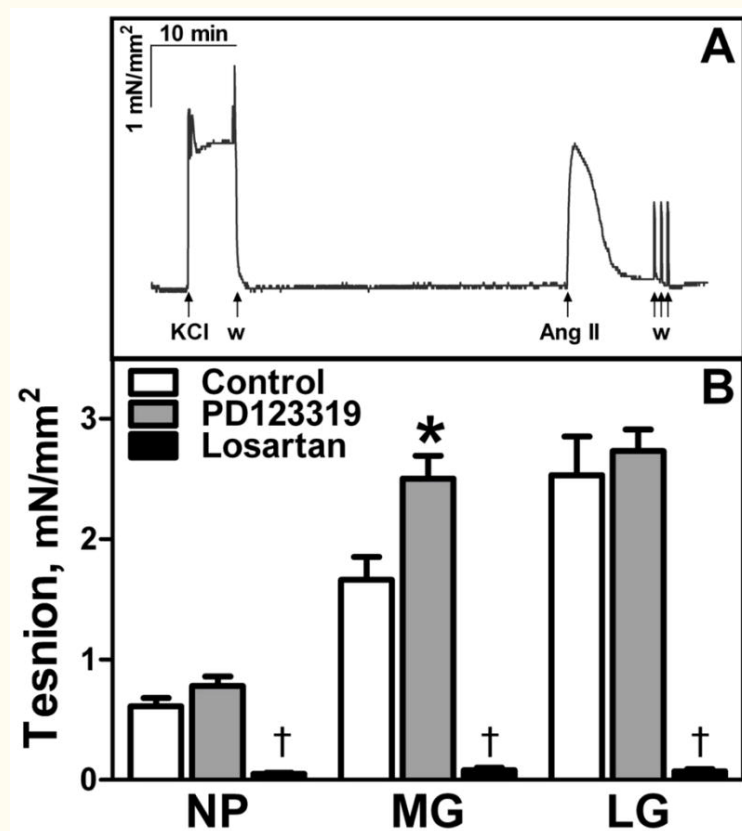


Figure 5

Contractile response to Ang-II in mouse UA. A. Representative trace showing the response to Ang-II in UA of a control pregnant mice at mid-gestation compared to the response to 62.5 mM KCl (w=wash). B. Absolute maximal response to Ang-II expressed as mN/mm^2 in control arteries, arteries pre-treated with PD123319 10^{-5} M and arteries pre-treated with losartan 10^{-5} M as indicated, in NP (n=5), MG (n=8) and LG (n=7) groups. Data are shown as mean \pm SEM. * $p < 0.05$ vs MG control, † $p < 0.05$ vs control and PD123319 treated arteries by ANOVA.

Response to acetylcholine

A cumulative concentration-response curve for acetylcholine was constructed by adding thirteen different concentrations (ACh 10^{-10} – 10^{-4} M) to vessels pre-constricted with 3×10^{-8} M U46619 or 80% of the maximal constriction, with each subsequent dose being introduced at 2-min intervals. In parallel experiments, different arterial segments were preincubated for 15 min with the nitric oxide synthase inhibitor L-NAME at a concentration of 10^{-4} M.

Solutions and drugs

Krebs buffer contained (in mM) NaCl 118.5, NaHCO₃ 25, KCl 4.7, KH₂PO₄ 1.2, MgSO₄ 1.2, CaCl₂ 2.5, and glucose 5.5 with a final pH of 7.4. In solutions used for testing KCl depolarizing effects, NaCl was replaced by an equimolar amount of KCl. All drugs and agonists used were obtained from Sigma Chemical Co. (St. Louis, MO).

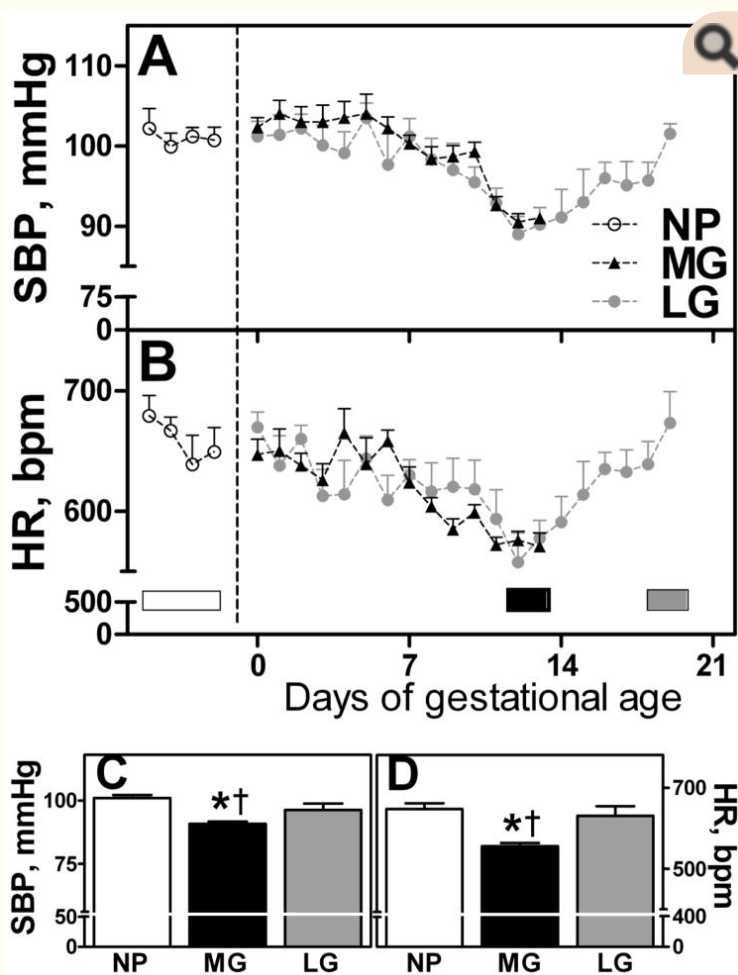
Data analysis

Myodata 2.02 (National Instruments Corporation, Denmark), Excel, and GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA) were used to analyze the data. Concentration-response curves for KCl, ACh and U-46619 were analyzed by fitting individual experimental data to a logistic curve to determine maximal response and sensitivity. The curve was of the form $Y = \text{bottom} + (\text{top} - \text{bottom}) / (1 + 10^{(\text{LogEC}_{50} - X) * \text{Hill Slope}})$ where X is the logarithm of the concentration and Y is the response, the EC₅₀ values reported are derived from these fits. The contractile response to KCl was expressed in mN/mm² as units of arterial wall tension (AWT) (AWT=force/2xlength of vessel). For each arterial segment the maximal response to KCl was calculated and the response to contractile agonists was expressed as percent of the corresponding maximal response to KCl. Relaxant responses were expressed as the percent of reduction of U46619-induced contraction. Sensitivity was expressed as pD₂ (pD₂= -log [EC₅₀]) with EC₅₀ being the concentration of agonist producing 50% of the maximal response. Data are expressed as mean ± SE. One-way analysis of variance (ANOVA) with Bonferroni's multiple comparisons was used to determine significant differences. A $p < 0.05$ was accepted as an indication of statistical significance.

RESULTS

Blood pressure and heart rate measurements

A reduction in SBP ([Figure 1A](#)) is evident at mid gestation, starting approximately at day 10 and reaching its peak at day 12 with a 10% maximal reduction in SBP compared to pre-pregnant values. In late gestation (days 18 and 19) SBP recovered to pre-pregnancy values. A similar pattern was observed for the recordings of HR with approximately 12% reduction in mid-gestation and recovery in late gestation ([Figure 1B](#)). The averages of values at mid gestation (days 12 and 13) showed a statistically significant reduction in SBP ([Figure 1C](#)) and HR ([Figure 1D](#)) compared to pre-pregnancy values whereas there were no such differences in late gestation.



[Figure 1](#)

Systolic blood pressure (SBP; A) and heart rate (HR; B) in non-pregnant (NP, n=6), mid gestation (MG, n=11) and late gestation

(LG, n=7) pregnant mice. Dotted vertical line indicates day of breeding. C and D: Data correspond to the average of 4 days for NP (white box), days 12 and 13 for MG (black box) and days 18 and 19 for LG (gray box). Data are shown as mean±SEM. * $p < 0.05$ vs NP and LG, † $p < 0.05$ vs LG by ANOVA.

In vitro experiments

As shown in [Table 1](#), isolated UA segments showed increasing external diameters from NP to MG and LG groups. The optimal diameters showed an increase of 23% and 73% in mid and late gestation compared to arteries from nonpregnant animals.

Table 1

Diameters and contractile responses to potassium chloride (KCl) and U46619 in isolated segments of mice uterine artery (UA).

	Non-pregnant (NP)	Mid-gestation (MG)	Late gestation (LG)
Animals/Arteries	5/20	8/30	7/28
Optimal diameter (OD), μm	166±5	205±16*	287±9*†
K_{MAX} , N/m	0.67±0.09	2.04±0.07*	2.75±0.36*†
KCl, pD ₂	1.73±0.03	1.78±0.04	1.76±0.04
U46619 _{MAX} , %K _{max}	114±4	110±5	101±3*
U46619, pD ₂	7.92±0.05	7.89±0.08	7.79±0.08

Optimal diameter refers to diameters of UA segments measured after the normalization procedure. Contractile responses for KCl are expressed as absolute values of tension in N/m, responses for U46619 are expressed as % of maximal KCl response (K_{MAX}); sensitivity is expressed as pD₂. Data are shown as mean±SEM.

* $p < 0.05$ vs. non-pregnant;

† $p < 0.05$ vs. mid gestation by ANOVA.

Response to KCl and U46619 Greater maximal contraction (K_{max}) values were observed in mid- or late-pregnant compared to nonpregnant animals (Table 1 and Figure 2A and 4, 204% and 310% in K_{max} respectively). No significant differences were observed in the sensitivity to KCl. The absolute values for the contractile response to U46619 followed a similar pattern with maximal tension values increasing progressively with gestation (0.79 ± 0.09 , 2.27 ± 0.11 and 2.54 ± 0.36 mN/mm² in NP, MG and LG animals respectively, Figure 4. Expressed as % of K_{max} the maximal response to U46619 was significantly lower in LG compared to the NP group. There were no changes in sensitivity at any time point (Table 1 and Figure 2B).

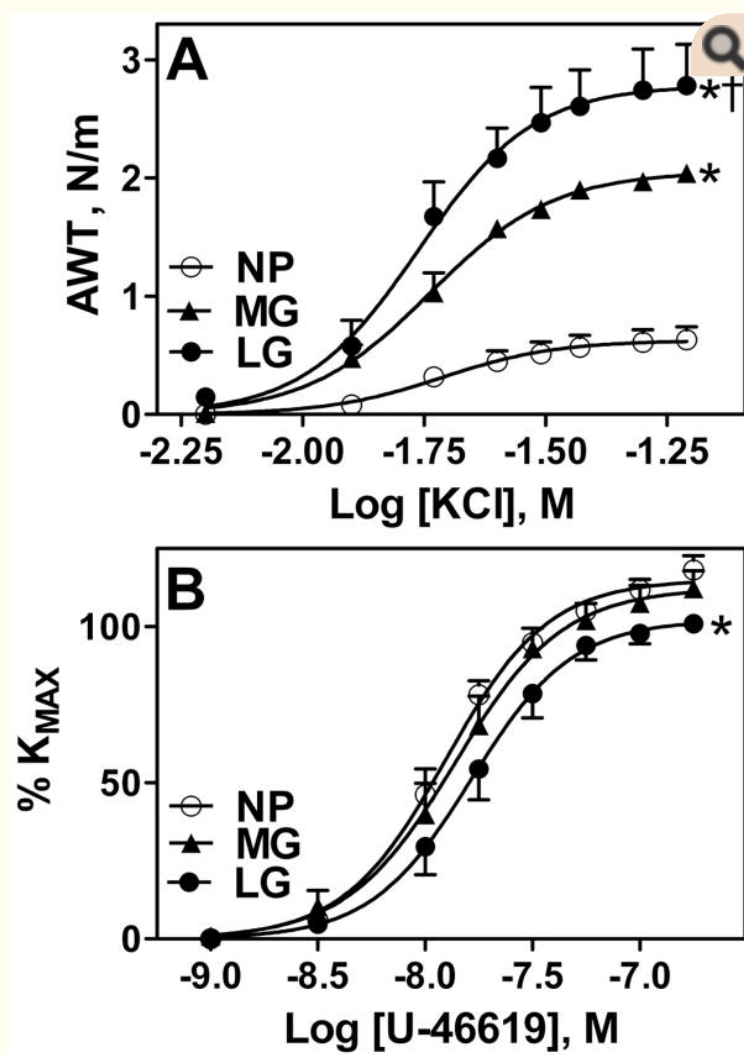
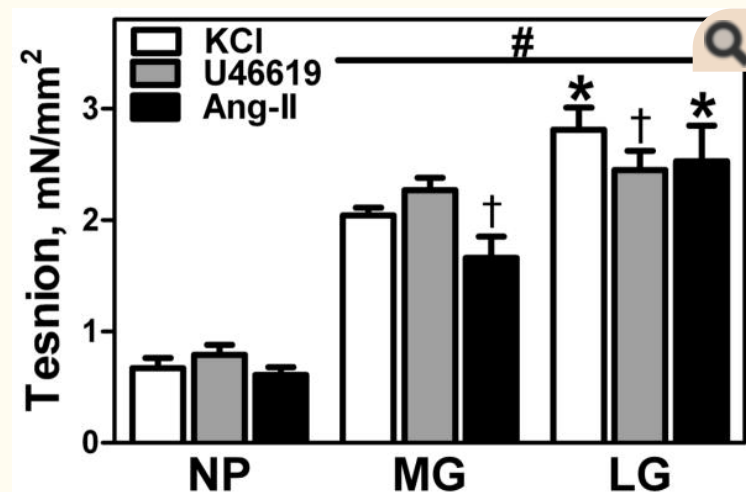


Figure 2

Potassium chloride (KCl)-induced (A) and U46619-induced (B) vasoconstriction in uterine arteries from non-pregnant (NP, n=5),

mid gestation (MG, n=8) and late gestation (LG, n=7) mice. Responses are expressed as absolute values of tension (AWT; arterial wall tension) in N/m (A) or as % of maximal KCl response (%K_{MAX}, B). Data are shown as mean±SEM. *p<0.05 vs NP, †p<0.05 vs MG, in maximal response by ANOVA.



[Figure 4](#)

Maximal contractile responses of isolated uterine artery (UA) during mouse pregnancy. Absolute maximal responses to KCl, U46619 and Ang-II expressed as mN/mm² in nonpregnant (NP, n=5), midgestation (MG, n=8) and late gestation (LG, n=7). Data are shown as mean±SEM. # p<0.05 vs NP values, *p<0.05 vs MG, †p<0.05 vs KCl.

Response to acetylcholine In arteries pre-constricted with a sub maximal dose of U46619 ($3 \times 10^{-8} \text{M}$) to achieve 80% of the maximal contraction, maximal relaxation to acetylcholine (ACh_{MAX}) was greater in mid and late gestation compared to nonpregnant state ([Figure 3A](#) and [Table 2](#)). Sensitivity to acetylcholine, expressed as pD₂, increased as gestation progressed ([Table 2](#)). Treatment with L-NAME diminished ACh_{MAX} in all the groups studied and decreased sensitivity in the mid- and late gestation groups ([Figure 3B](#) and [Table 2](#)).

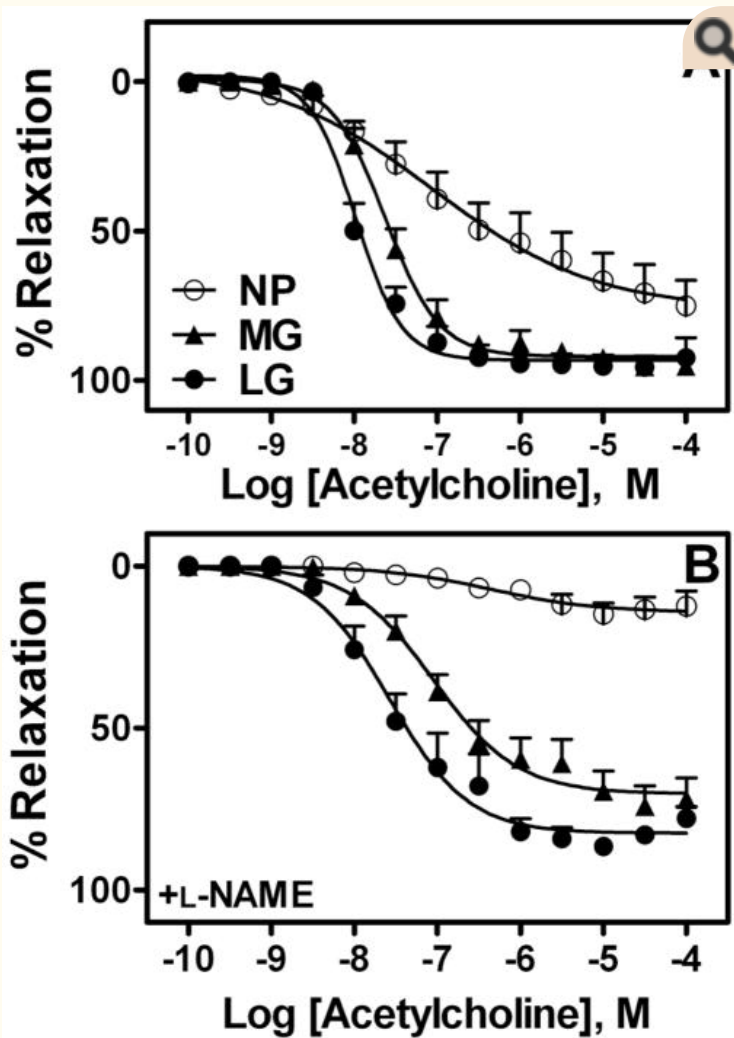


Figure 3

Acetylcholine-induced relaxation in NP, MG and LG uterine arteries pre-constricted with 3×10^{-8} M U46619. Responses are expressed as percentage of the contraction response. A; response in control arteries. B; response in arteries pre-treated with 10^{-4} M L-NAME. Data are shown as mean \pm SEM. * $p < 0.05$ vs NP by ANOVA.

Table 2

Parameters of the ACh response in isolated segments of mice uterine artery (UA).

Non-pregnant (NP)	Mid-gestation (MG)	Lat
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	Control	+ L- NAME	Control	+ L- NAME	Con
ACh _{MAX} , %	79±6	18±2 [‡]	91±3 [*]	72±6 [‡]	94
ACh pD ₂	6.62±0.34	6.49±0.23	7.62±0.09 [*]	6.98±0.18 [‡]	7.9±0.18

Maximal relaxation (ACh_{MAX}) and sensitivity (ACh pD₂) to acetylcholine in the UA of non pregnant, mid gestation and late gestation pregnant mice. Values for control arteries and arteries treated with the nitric oxide synthase inhibitor (+L-NAME 10⁻⁴M) are shown.

*p<0.05 vs non pregnant;

†p<0.05 vs mid gestation;

‡p<0.05 vs control by ANOVA.

Response to Ang-II As shown in [Figure 5A](#) 10⁻⁷M Ang-II elicits a transient response. As was the case for KCl and U46619, absolute contractile response to Ang-II was increased during pregnancy with values of 0.5±0.1, 1.7±0.3 and 2.6±0.5 mN/mm² in NP, MG and LG animals respectively ([Figure 4](#)). Pre-incubation with the AT2 receptor blocker PD123319 (10⁻⁵ M) induced a greater contraction in the MG group compared to the controls ([Figure 5B](#)). No effects of AT2 receptor blockade were observed in NP or LG groups. Pre-incubation of the arterial segments with losartan 10⁻⁵ M, to inhibit AT1 receptor-mediated responses, abolished the Ang-II response in all three groups.

DISCUSSION

In this study we measured blood pressure and heart rate during gestation in wild type C57BL/6J mice and vascular reactivity in isolated uterine arteries (UA). Our findings of a lower BP at mid pregnancy agreed with previous reports ([25;34](#)) while heart rate responses seem more variable ([28;29;34;35](#)). Given the importance of Ang-II responses in the uteroplacental circulation during pregnancy and the differing contributions of the AT1 and AT2 receptors in mediating this response, we studied the role of the AT2 receptor in modulating UA Ang-II contractile response. Our results showed that pregnancy increased the contractile response to Ang-II in the mouse UA and that this contraction was further increased in the presence of the AT2 inhibitor PD123319 at mid-gestation. We

interpreted these results as supporting the likelihood that increased AT2-mediated activity opposed the contractile effects of Ang-II and contributed to enhanced UA vasodilatation. Suggesting that AT2 receptor-mediated signaling might play a more general role in pregnancy-associated vasodilatation was that the time at which the greater inhibitory effect of PD123319 was observed coincided with that at which systemic blood pressure was lowest.

The UA undergoes significant structural and functional changes during pregnancy (6). In particular the UA doubles in diameter in humans and other species (2), and increased responses to KCl have been observed in sheep arteries (8). Similarly we observed increased diameters and greater responses to KCl in UA from pregnant vs. nonpregnant mice. Our values for maximal response to KCl at late gestation (2.75 ± 0.36 mM/mm²) agree with those reported for the mice UA at equivalent gestational age (~ 2.5 mM/mm²) (21). Increased KCl-mediated contraction during pregnancy suggests the presence of more vascular smooth muscle cells, which in turn is likely due to the pregnancy-associated increase in sensitivity of UA smooth muscle cells to proliferative stimuli (7). Unique to pregnancy is that these changes lead to outward hypertrophic remodeling with increased cross-sectional area (6;36). Given these changes in smooth muscle content, we expressed the tension developed as % of the maximal response to KCl in order to allow the evaluation of agonist responses independent of the amount of smooth muscle per unit of surface area. Therefore we interpret the lower contractile response to U46619 in LG arteries as indicating an attenuation of UA constrictor responses; this is similar to previous observations in rats (24), guinea pigs (37) and mice (29).

The incomplete inhibition of the vasodilator response to acetylcholine observed in the present study following L-NAME treatment in pregnant UA suggests that mechanisms other than nitric oxide (NO) influence UA vasodilatation during murine pregnancy. The importance of NO production during pregnancy has been widely recognized. However, since knockout mice for any of the NO synthase (NOS) isoforms do not develop hypertension (38), it appears likely that mechanisms other than NO are also involved. Such additional vasodilators are likely to be cyclo-oxygenase products, specifically PGI₂ (22;39) as well as endothelium-derived hyperpolarizing factor (EDHF) (40;41). A new observation from the present study is that AT2-mediated vasodilatation may also be involved.

The UA exhibited a different response to U46619 and Ang-II in

during pregnancy; whereas the U46619 maximal contraction was lower in LG, we interpret the lower Ang-II in MG as an indication of an Ang-II-specific mechanism activated earlier in gestation. The vasoconstrictor actions of the Ang-II system have been well studied during pregnancy but comparatively less attention has been devoted to its AT2-mediated vasodilatory effects. During human pregnancy the systemic and uterine circulations became less responsive to the contractile effects of Ang-II despite the increases occurring in several components of the RAS. While many factors influence the RAS, our results showing an increased inhibitory effect of PD123319 on Ang-II stimulation at mid-gestation suggests a role for increased AT2-mediated signaling that acts to oppose AT1-mediated UA vasoconstriction at mid-pregnancy. Consistent with the results reported here are studies showing that PD123319 blocks the mid-gestation decrease in BP in mice and that AT2-receptor deficient strains lack this normal mid-pregnancy BP fall (25;26). The availability of AT1 and AT2 receptor knockout mice (KO) creates the possibility of further evaluating the role of AT2-mediated signaling in lowering peripheral vascular resistance during pregnancy. Needed are studies of uterine blood flow and vascular reactivity in these KO strains to establish the mechanisms whereby the AT2-receptor-mediated vasodilatation influences UA and systemic vascular control during pregnancy. Information as to whether AT2 receptor signaling is disrupted in preeclampsia would enlarge our understanding of this still poorly-understood disease, known to be a major cause of maternal and infant morbidity and mortality. A role for AT2-mediated signaling in decreasing BP and raising UA blood flow might also be a potentially important target for treating the uteroplacental ischemia characteristic of this disorder (42;43).

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