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Renal natural killer cell activation and mitochondrial oxidative stress; new mechanisms in AT1-AA mediated hypertensive pregnancy

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ABSTRACT

Women with preeclampsia (PE) have increased mean arterial pressure (MAP), natural killer (NK) cells, reactive oxygen species (ROS), and agonistic autoantibodies to the angiotensin II type 1 receptor (AT1-AA). AT1-AA's administered to pregnant rodents produces a well-accepted model of PE. However, the role of NK cells and mitochondrial reactive oxygen species (mtROS) in AT1-AA mediated hypertension during pregnancy is unknown. We hypothesize that AT1-AA induced model of PE will exhibit elevated MAP, NK cells, and mtROS; while inhibition of the AT1-AA binding to the AT1R would be preventative. Pregnant rats were divided into 4 groups: normal pregnant (NP) (n = 5), NP + AT1-AA inhibitory peptide (NP +'n7AAc') (n = 3), NP + AT1-AA infused (NP + AT1-AA) (n = 10), and NP + AT1-AA +'n7AAc' (n = 8). Day 13, rats were surgically implanted with mini-pumps infusing either AT1-AA or AT1-AA +'n7AAc'. Day 19, tissue and blood was collected. MAP was elevated in AT1-AA vs. NP (119 ± 1 vs. 102 ± 2 mmHg, $p < 0.05$) and this was prevented by 'n7AAc' (108 ± 3). There was a 6 fold increase in renal activated NK cells in AT1-AA vs NP (1.2 ± 0.4 vs. 0.2 ± 0.1% Gated, $p = 0.05$) which returned to NP levels in AT1-AA +'n7AAc' (0.1 ± 0.1% Gated). Renal mtROS (317 ± 49 vs. 101 ± 13% Fold, $p < 0.05$) was elevated with AT1-AA vs NP and was decreased in AT1-AA +'n7AAc' (128 ± 16, $p < 0.05$). In conclusion, AT1-AA's increased MAP, NK cells, and mtROS which were attenuated by AT1-AA inhibition, thus highlighting new mechanisms of AT1-AA and the importance of drug therapy targeted to AT1-AAs in hypertensive pregnancies.

1. Introduction

Preeclampsia (PE) is a hypertensive disorder that is generally characterized as new onset hypertension occurring during the 3rd trimester of pregnancy [1–4]. It is the leading cause of preterm birth, morbidity, and mortality for both the mother and the fetus [4]. The effects of preeclampsia can result in organ damage and dysfunction, resulting in chronic kidney disease, cardiovascular disease, stroke, and metabolic syndrome during pregnancy and/or postpartum [1,3,5–10]. As of today, there is no cure for preeclampsia except for the delivery of the fetal placental unit.

The genesis of the PE is unknown, but is believed to start at the level of the placenta [11]. Many circulating factors increase in response to placental ischemia which contribute to an increase in blood pressure and organ (brain, liver, and kidney) damage during PE. A few of these factors include agonistic angiotensin II type 1 receptor autoantibody (AT1-AA), inflammatory cytokines and cells and oxidative stress [2–4,11–13]. Wallukat et al, discovered that AT1-AAs were elevated in women with PE and that they bind to a very specific seven amino acid (7AA) sequence activating the AT1 receptor [14]. Zhou et al isolated AT1-AAs from preeclamptic patients and injected them into pregnant rats and demonstrated that the AT1-AA elicited many features of PE such as hypertension, intrauterine growth restriction, renal pathology, and inflammatory cytokines. We have demonstrated that rat AT1-AAs

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isolated from reduced uterine perfusion pressure (RUPP) rat model of PE cause hypertension, oxidative stress, increased renal artery resistance, sFlt-1, and endothelin-1 when infused into pregnant rats [15,22–30]. All of these features can be improved with angiotensin II receptor blockers (ARBs), such as losartan. However, any blockade of the endogenous renin angiotensin system is contraindicated during pregnancy due to toxicity toward the fetus, thus indicating the importance of drug discovery targeting the actions of the AT1-AA during PE.

In a recent study, we used a modified inhibitory peptide against the AT1-AA ('n7AAc'), which improved blood pressure and renal function, and lowered circulating factors associated with PE, such as ET-1, sFlt-1, and isoprostanes in RUPP rats [31]. In addition, we observed an increase in NO bioavailability in RUPP rats treated with ('n7AAc'). These data suggest that the decrease in these circulating factors decreases oxidative stress, which in return increased NO bioavailability [31]. Women with preeclampsia have an increase in oxidative stress [2,4,22]. Although mitochondria are a major source of reactive oxygen species (ROS) only a few studies have examined a role for mitochondrial oxidative stress (mtROS) during PE [40–47].

Recent studies show the importance of cytolytic NK cells in PE [2,32–37]. We recently demonstrated that NK cells were increased in the RUPP rat model of PE, and that depletion of NK cells reduced circulating and placental inflammatory cytokines and improved hypertension [31,38]. Moreover, we demonstrate that NK cells are decreased in RUPP rats treated with 'n7AAc' [31]. NK cells are activated by inflammatory cytokines and binding to IgG-bound cells causing cytotoxicity and oxidative stress. One mechanism by which NK cells induce cytotoxicity is through impaired mitochondrial function, thereby suggesting this to be one mechanism where by NK cells could mediate renal and placental injury in PE. Thus, the purpose of this study was to examine the role of AT1-AAs to cause NK cell activation and mtROS and to determine the efficacy of AT1-AA inhibition to block AT1-AA induced hypertension, elevated NK cells, and mtROS in pregnant rats.

2. Methods

All animal protocols were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Mississippi Medical Center. Pregnant Sprague Dawley rats purchased from Harlan Sprague Dawley Inc. (Indianapolis, IN) were used in this study. Rats were placed on a normal diet with free access to water and housed with a 12 h light and dark cycle with a temperature-controlled room (75 °F). All experiments performed were in accordance with the National Institutes of Health guidelines for use and care of animals.

2.1. Administration of AT1-AA with or without 'n7AAc'

On day 13 of gestation, pregnant rats were anesthetized with isoflurane and osmotic mini-pumps infusing the AT1-AA (1:40 dilution) purified from RUPP rats (Alzet Model 2001, Durect Corp, Cupertino, CA) were implanted intraperitoneally as previously described [29].Previous studies from our lab have shown that this dose of AT1-AA (1:40) administered to pregnant rats causes an increase in blood pressure and other aspects of PE [15,29]. One group of rats received the AT1-AA alone and a second group received the AT1-AA premixed with the 'n7AAc' at a dose of 2 μg/μl [31]. These groups were compared to normal pregnant and normal pregnant rats received the'n7AAc' at a dose of 2 μg/μl. The dose is based on our previous publication in which 'n7AAc' attenuates many aspects of PE observed in the RUPP rat [31]. Therefore, in this study pregnant Sprague Dawley rats were divided into 4 groups: Normal Pregnant (NP, n = 5), NP +'n7AAc' (n = 3), AT1-AA (AT1-AA, n = 10) infused rats, and AT1-AA + AT1-AA inhibitory peptide (AT1-AA +'n7AAc', n = 8).

2.2. Effect of 'n7AAc' on blood pressure and fetal outcome in AT1-AA induced hypertensive pregnant rats

On day 18 of gestation, using isoflurane anesthesia, catheters were inserted into the carotid artery and tunneled through the back of the neck and utilized to measure conscious mean arterial blood pressure (MAP) on day 19 of gestation. On day 19 of gestation, conscious MAP was determined after placing the rats in individual restraining cages. [31] Briefly, arterial pressure was monitored with a pressure transducer (Cobe III transducer CDX Sema) and recorded continuously for 45 min after a 30-min stabilization period. Subsequently, while under isoflurane anesthesia, blood and tissue samples were collected. Pup weights were obtained and placentas and kidneys were harvested, weighed, and stored in −80 °C for further use.

2.3. Effect of 'n7AAc' on placental and renal activated NK cells in AT1-AA induced hypertensive pregnant rats

At the time of harvest, kidneys and placentas were collected. All lymphocytes will be isolated by centrifugation on a cushion of Ficoll-Hypaque (Lymphoprep, Accurate Chemical & Scientific Corp., Westbury, NY), and counted. For flow cytometric analysis, 1×10^6 cells were incubated for 30 min at 4 °C with antibodies against rat Anti-Natural Killer Cell Activation Structures (ANK61) or rat Anti-Natural Killer Cell antibody (ANK44) (AbCam, Cambridge, MA). ANK61 binds to all NK cells, while ANK44 is only expressed on stimulated, cytotoxic NK cells. After washing, cells were labeled with secondary Fluorescein isothiocyanate (FITC; AbCam) antibody for 30 min at 4 °C. As a negative control for each individual rat, cells were treated exactly as described above except they were incubated with isotype controls antibodies conjugated to FITC alone. Subsequently, cells were washed, fixed, and resuspended in 500 μL of Rosswell Park Memorial Institute medium (RPMI) and analyzed for single staining on a Gallios flow cytometer (Beckman Coulter, Brea, CA). Lymphocytes were gated in the forward and side scatter plot. Cells that stained as ANK61 + will were designated as NK cells. Cells that stain as ANK44+ were designated as activated NK cells. The percent of positive stained (Ank44+/Ank61+) cells above the negative control was collected for individual rats and the mean values for each experimental group were taken [48].

2.4. Effect of 'n7AAc' on placental and renal mitochondrial oxidative stress in AT1-AA induced hypertensive pregnant rats

Placental and renal mitochondrial hydrogen peroxide levels, a marker of mitochondrial oxidative stress, was measured with fluorescence using the amplex red ultra (A36006, ThermoFisher Scientific, Eugene, OR) solution with intact mitochondria. To isolate intact mitochondria, placentas were isolated from pregnant rats on day 19 of pregnancy and was homogenized in a Mito buffer I solution consisting of 250 mM Sucrose, 10 mM HEPES, 1 mM EGTA, 0.1% BSA at a pH 7.2. The homogenate was then subjected to several centrifugation steps to isolate intact mitochondria. First homogenates were centrifuged at 4000 RPM for 3 min, then centrifuged twice at 10,000 RPM for 10 min, and finally centrifuged at 10,000 RPM for 10 min with a Mito buffer II solution consisting of 250 mM Sucrose, 10 mM HEPES, 0.1% BSA at a pH 7.2. The intact mitochondria homogenate was incubated with 0.2 M succinate, 10 mM amplex red solution, 4 units/ml horseradish peroxidase, and 40 units/ml of CuZn superoxide dismutase for 30 min. Hydrogen peroxide levels was measured in each sample in units/min/mg of protein and normalized to normal pregnant rats. Data in the graphs shows the increase in percent fold of hydrogen peroxide levels in normal pregnant rats compared to that of treated rats for 30 min.

2.5. Statistical analysis

All data and results are presented as means ± SE. Data were

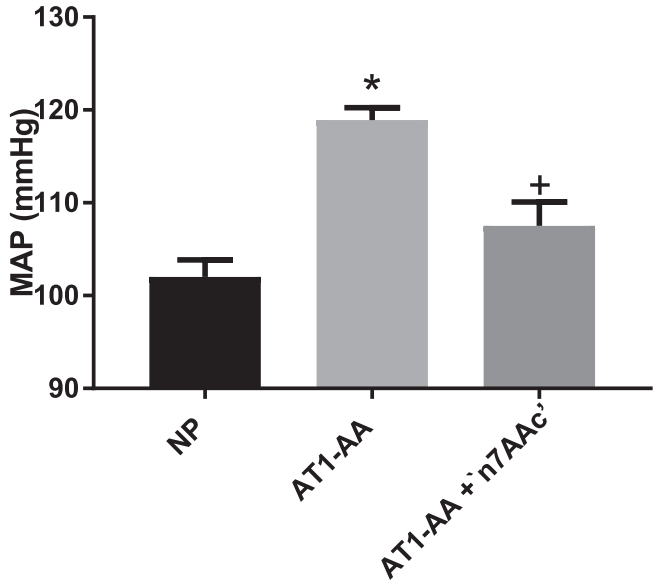

Fig. 1. MAP was elevated in AT1-AA infused vs. normal pregnant rats (NP) which was attenuated in AT1-AA + 'n7AAc' treated rats. No difference in MAP was noted between NP + 'n7AAc' and NP rats. Statistical differences were achieved using one-way ANOVA with Tukey's post hoc analysis, $^{*}p < 0.05$ vs NP and $^{+}p < 0.05$ vs. AT1-AA.

analyzed by one way ANOVA with Tukey's post hoc analysis or by student *t-test* comparing each group to normal pregnant (control) values using Graphpad Prism 6 software (GraphPad Software, La Jolla, CA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Effect of 'n7AAc' on blood pressure and fetal outcome in AT1-AA induced hypertensive pregnant rats

MAP was elevated in AT1-AA treated rats compared to NP rats (119 ± 1 vs. 102 ± 2 mmHg, $p < 0.05$) (Fig. 1) The increase in MAP was attenuated with AT1-AA inhibition peptide ('n7AAc') (108 ± 3 vs. 119 ± 1 mmHg, $p < 0.05$) (Fig. 1). There was no change in MAP between NP + 'n7AAc' and NP rats (104 ± 2 vs. 102 ± 2 mmHg) or between NP + 'n7AAc' and AT1-AA + 'n7AAc' rats (104 ± 2 vs. 108 ± 3 mmHg) (Fig. 1).

No change was observed in pup weight among the groups (Fig. 2A). However, there was a decrease in the number of live pups between AT1-AA treated and NP rats (12 ± 1 vs. 15 ± 2, $p < 0.05$) (Fig. 2B). Administration of 'n7AAc' had no effect on the number of live pups (15 ± 0) (Fig. 2B). Maternal body, placental, and kidney weight was not different between NP, NP + 'n7AAc', AT1-AA infused, and AT1-AA + 'n7AAc' rats (Fig. 3).

3.2. Effect of 'n7AAc' on placental and renal activated NK cells in AT1-AA induced hypertensive pregnant rats

Placental activated (cytolytic) NK cells (0.67 ± 0.21 vs. 0.26 ± 0.11% gated, NS) trended to increase with AT1-AA administration vs. NP rats and was unchanged with 'n7AAc' (Fig. 4A). However, renal activated NK cells were increased in AT1-AA rats vs. NP rats (1.21 ± 0.41 vs. 0.21 ± 0.11% gated, $p = 0.05$) (Fig. 4B) which was attenuated with 'n7AAc' (0.12 ± 0.06). Thus our study shows that AT1-AAs may have a greater effect to stimulate NK cells in the kidney compared to the placenta and that this can be attenuated by administration of 'n7AAc'. Due to a lack of change in MAP and fetal weight between NP + 'n7AAc' and NP rats, no other molecular analysis for flow cytometry was performed on NP + 'n7AAc'.

3.3. Effect of 'n7AAc' on placental and renal mitochondrial oxidative stress in AT1-AA induced hypertensive pregnant rats

In the placenta, mtROS (167 ± 28 vs. 101 ± 14% Fold, $p = 0.09$) had a tendency to increase with AT1-AA administration vs. NP rats (Fig. 4C). There was a 3 fold increase in renal mtROS in AT1-AA infused rats vs. NP rats (317 ± 50 vs. 101 ± 13% Fold, $p < 0.05$) (Fig. 4D) which was attenuated with administration of 'n7AAc'. Interestingly, these data correlate with the increase in renal NK cells which can also be inhibited by 'n7AAc'.

4. Conclusion

The new findings of this study are that AT1-AA induced hypertension during pregnancy occur with renal NK cell activation and renal mtROS, which can be attenuated with an inhibitory peptide designed to target the AT1-AA. In addition this study also showed that the 'n7AAc' does not cause deleterious effects in pregnant rats or their offspring. This is evident by no change in blood pressure, pup weight, number of

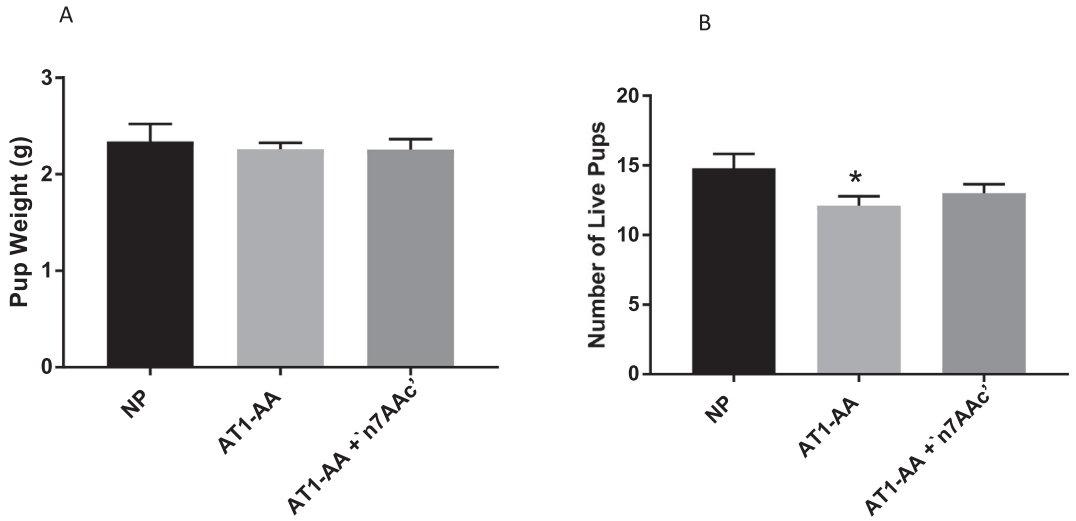

Fig. 2. A) No difference in pup weight was observed between NP, NP + 'n7AAc', AT1-AA, and AT1-AA + 'n7AAc' rats. B) Number of live pups was decreased for AT1-AA vs NP rats. Statistical differences were achieved using one-way ANOVA with Tukey's post hoc analysis, $^{*}p < 0.05$ vs NP and $^{+}p < 0.05$ vs. AT1-AA.

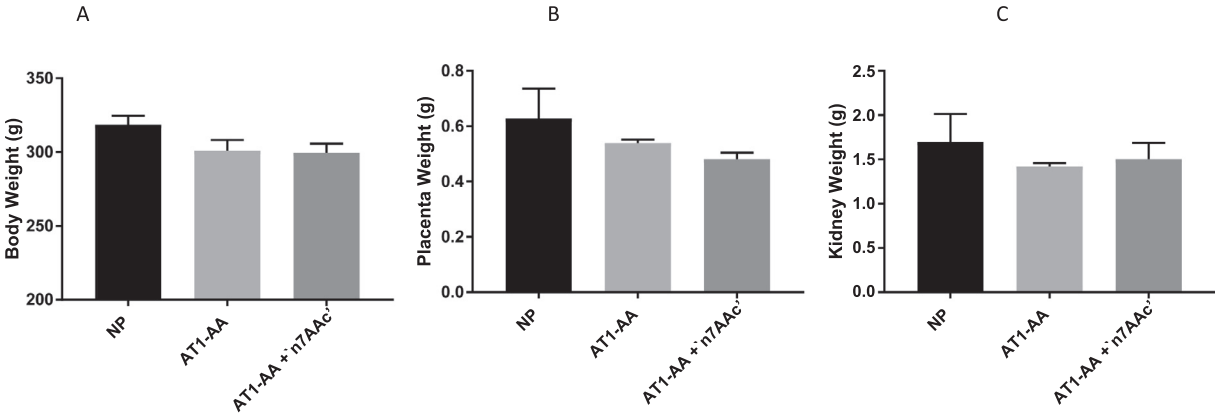

Fig. 3. No change in A) maternal body weight, B) placenta weight, and C) kidney weight was observed among NP, NP + 'n7AAc', AT1-AA, and AT1-AA + 'n7AAc' rats.

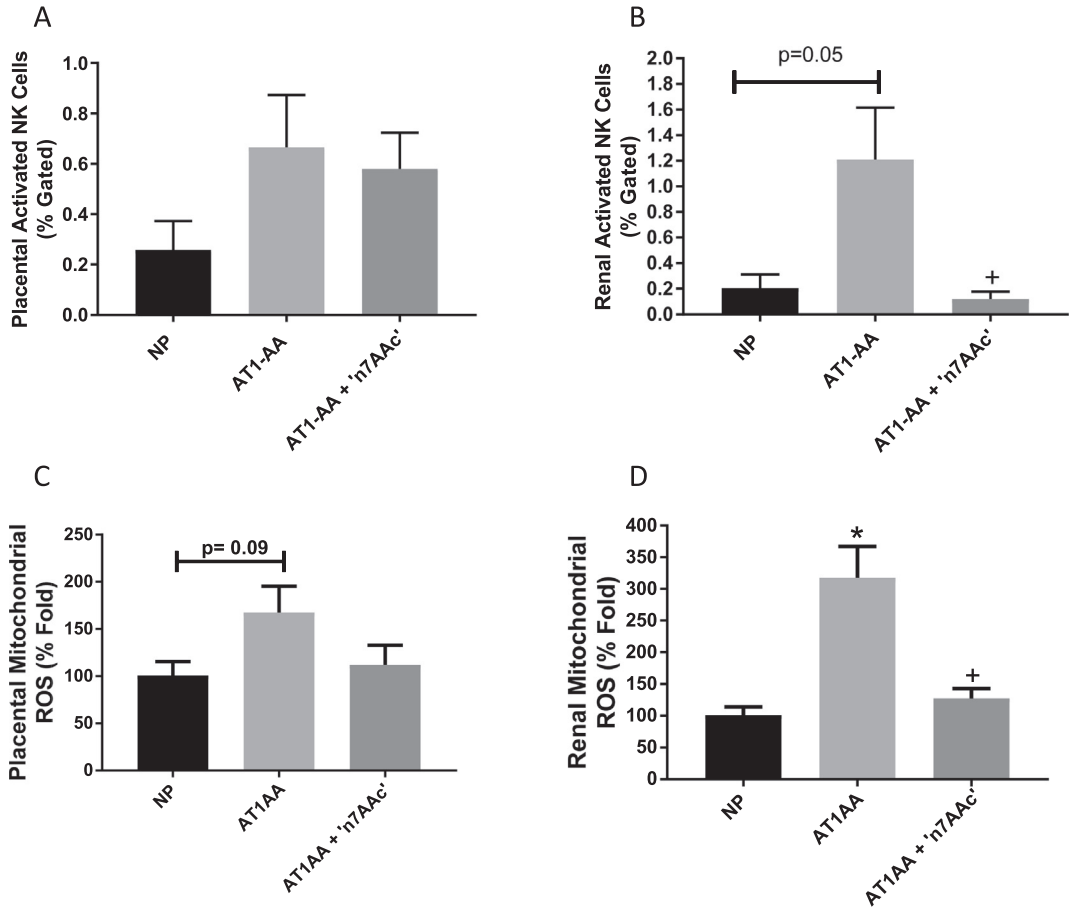

Fig. 4. A) There was a tendency for placental activated NK cells to increase in AT1-AA vs NP rats (ns.) B) Renal activated NK cells were elevated in AT1-AA vs NP rats ($p = 0.05$). AT1-AA + 'n7AAc' treated rats exhibited a decrease in activated NK cells in comparison to AT1-AA rats. C) Placental mtROS was elevated in AT1-AA vs NP rats ($p = 0.09$). D) Renal mtROS was elevated in AT1-AA vs. NP rats which was attenuated in AT1-AA + 'n7AAc' treated rats. Statistical differences were achieved using one-way ANOVA with Tukey's post hoc analysis, $^{*}p < 0.05$ vs NP and $^{+}p < 0.05$ vs. AT1-AA.

live pups, maternal body and kidney weight, and placental weight in comparison to normal pregnant rats. Several studies by Xia *et al.* and our laboratory have shown that AT1-AAs cause a decrease in trophoblast invasion, calcium mobilization, intrauterine growth restriction, proteinuria, renal pathology, and hypertension [19,22,49,50]. Additionally, studies have shown that AT1-AAs increase ET-1, sFlt-1, renal afferent arteriolar vasoconstriction, and oxidative stress; thereby suggesting that the AT1-AA has direct and indirect vascular actions to cause vasoconstriction on vessels [9,15,19,22,24,25,29,49,50]. Studies with ARB treatment alleviates most, if not all, of these symptoms [22,51]. However, ARBs are toxic to the fetus during pregnancy and are contraindicated, suggesting that a more specific inhibitor of AT1-AA induced PE symptoms is essential for moving this field forward. Therapies targeted to the AT1-AA to keep it from binding to the AT1 receptor have previously been performed by the laboratory of Yang Xia, where they administered a linear seven amino acid sequence peptide corresponding to the binding site on the AT1 receptor to pregnant mice receiving human AT1-AA. These groundbreaking studies showed 7aa

blockade of the AT1-AA can improve hypertension and many factors associated with PE [22,31,49,50]. In a separate study performed by Li et al, using the retro-inverso D-amino acid epitope-mimetic peptide of the AT1R epitope, a second form of specific AT1-AA blockade improved hypertension and decreased the vasoconstriction of isolated arterioles treated with ANG II, rabbit anti-AT1R sera, or AT1-AA [52]. The retro-inverso D-amino acid epitope-mimetic peptide had an increased half-life in-vitro that remained intact 2hrs later in human serum compared to the linear peptide that was completely degraded in 45 min [52]. This study further highlights the importance of therapy against the AT1-AA.

In the current study we examined the effects of a newly constructed, modified AT1-AA inhibitory peptide premixed with the AT1-AA to determine if epitope binding could negate AT1-AA induced hypertension. As stated, we have previously shown this peptide to prevent maternal hypertension, anti-angiogenic and vasoconstrictive factors, improve systemic NO bioavailability, decrease NK cell activation, and improve oxidative stress in response to placental ischemia in the RUPP rat model [31]. This peptide used in both of our studies is different from the linear peptide used by others through a modification known as capping of the N and C terminus of the peptide [19,22,49,50,52]. Protein capping is a process commonly used to increase peptide half-life and to protect exogenous peptides from protein lysis and degradation when used in the whole animal. The blockade of the AT1-AAs with this capped peptide in this study decreased hypertension, NK cell activation, and mtROS, thereby supporting the causative role of AT1-AAs not only in hypertension during pregnancy but also to stimulate other PE symptoms such as NK cells and mtROS. In addition, this study showed that the total number of pups was decreased with AT1-AA infusion, which was prevented by AT1-AA inhibition.

Women with PE also have increased inflammation and oxidative stress, partly due to an increase in activated cytolytic NK cells [32,33,38,39]. Studies from Dr. Cornelius' lab, have shown that activated NK cells are not only elevated in the RUPP rat model of PE but that they are instrumental in causing hypertension and release of proinflammatory cytokines such as TNF alpha and IL-17 [38]. Moreover, studies from her lab demonstrated the importance of NK cells in causing intrauterine growth restriction [38]. In this study we showed that activated NK cells in both the kidney and placenta were increased in AT1-AA infused rats, which was improved with the inhibitory peptide.

Activated NK cells produce cytokines, perforin, and granzymes that will increase mtROS [38,39]. Very few studies have looked at the role of mitochondria dysfunction and ROS in pregnancy [40–47]. In this study we are the first to show that kidney and placental mtROS are elevated in AT1-AA infused rats and that AT1-AA inhibition lowered renal mtROS and NK cells. The exact mechanism as to how the AT1-AA can activate NK cells is still being investigated, however NK cells are activated by binding to the Fc region of an IgG, which is the immunoglobulin type of the AT1-AA. Therefore we believe the AT1-AA could serve as a stimulus for activating NK cells in the placenta and kidney during pregnancy. Future studies will further investigate the role of AT1-AA to cause NK cell activation in the kidney and placenta and how these cells effect blood pressure during pregnancy. Nevertheless, these novel findings have a greater implication in PE, in which it proposes that AT1-AA activated NK cells and mtROS play a key role in hypertension and the phenotype of PE.

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Conflict of interest/disclosure statement

There are no disclosures or conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2018.11.004.

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Further reading

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