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## The role of Agonistic Autoantibodies to the Angiotensin II Type 1 Receptor (AT1-AA) in Pathophysiology of Preeclampsia

Nathan Campbell<sup>1</sup>, Babbette LaMarca<sup>1,2</sup>, and Mark W. Cunningham Jr.<sup>1</sup>

<sup>1</sup>Depart. of Pharmacology & Toxicology, University of Mississippi Medical Center, Jackson, MS

<sup>2</sup>Depart. Of Obstetrics and Gynecology, University of Mississippi Medical Center, Jackson, MS

### Abstract

Preeclampsia is the leading cause of death and morbidity world-wide for the mother and fetus during pregnancy. Preeclampsia does not only effect the mother and the baby during pregnancy, but can also have long-term effects, such as the increase risk of hypertension and cardiovascular disease, on the offspring and the postpartum mother later in life. The exact cause of preeclampsia is unknown, but women with preeclampsia have elevated concentrations of agonistic autoantibodies against the angiotensin II type 1 receptor (AT1-AA). These AT1-AA's through multiple studies have shown to play a significant role in the pathology and possible genesis of preeclampsia. This review will discuss the discovery of AT1-AAs and the role of AT1-AAs in the pathophysiology of preeclampsia. This review will also discuss future therapeutic approaches towards the AT1-AA to prevent adverse pregnancy outcomes. Furthermore, we will examine the relationship between AT1-AA induced hypertension associated with increase oxidative stress, antiangiogenic factors (such as soluble fms-related tyrosine kinase-1 (sFlt-1), endothelin-1 (ET-1), inflammation, endothelial dysfunction, and reduced renal function. Understanding the pathological role of AT1-AAs in hypertensive pregnancies is important as we search for novel therapies to manage preeclampsia.

### Keywords

Preeclampsia; angiotensin II type 1 receptor autoantibody (AT1-AA); oxidative stress; renal function; endothelin

### The Role of AT1-AA in Pathophysiology of Preeclampsia

Preeclampsia (PE) is defined as new onset hypertension usually occurring during the third trimester of pregnancy.<sup>1,2</sup> The incidence of PE worldwide ranges from 2–10%, with a higher incidence in developing countries ranging from 1 case per 100 pregnancies to 1 case per 1700 pregnancies.<sup>3</sup> The incidence in developed countries, such as those in North America and Europe, have a similar incidence of PE ranging from 5–7 cases per 10,000 deliveries.<sup>3</sup>

**Corresponding Author:** Babbette LaMarca, PhD, Professor, Thesis Director, Division of Maternal Fetal Medicine, Department of Pharmacology and Toxicology, Department of Obstetrics and Gynecology, Center for Excellence in Renal and Cardiovascular Research, University of Mississippi Medical Center, Jackson MS, 39216, Phone: 601-815-1430, Fax: 601-815-1446, bblamarca@umc.edu.

In the USA It is estimated that between 3–5% of births are affected every year by PE.<sup>1</sup> The differences incidences of preeclampsia according to the world health organization (WHO) is due to the lack of access to health care.<sup>3</sup> PE is the leading cause of death for both the mother and the fetus during pregnancy.<sup>1</sup> Women with PE have elevated concentrations of angiotensin II type 1 receptor agonistic autoantibodies (AT1-AA), antiangiogenic factors (such as sFlt1 and s-endoglin), oxidative stress, inflammation, reduced renal function, endothelial dysfunction, and increased sensitivity to Angiotensin II (ANGII) (Figure 1).<sup>1,2,4–11</sup> The initiating event in preeclampsia is believed to be reduced placental perfusion due to shallow trophoblast invasion of the uterine spiral arterioles.<sup>2</sup> This reduction in blood flow to the fetus, decreases the flow of essential nutrients which can result in intrauterine growth restriction.<sup>1</sup> Such restriction of the placenta contributes to placental ischemia, which may result in oxidative stress, inflammation, and antiangiogenic factors contributing to hypertension, maternal end organ damage, and fetal demise.<sup>2</sup> As of today there is no cure for PE, except for the delivery of the fetal placental unit.<sup>2</sup> Thus drug discovery examining new pathways in PE are warranted to help these women. One such pathway worth further exploration is the AT1-AA.

### AT1-AA Characterized

The angiotensin II type 1 receptor autoantibody (AT1-AA) was characterized in 1999 by a group of researchers in Germany.<sup>4</sup> This group characterized the AT1-AA after isolation of total immunoglobulins from the serum of preeclamptic and normal pregnant women. After the isolation of these antibodies from the PE serum, they showed that these antibodies could stimulate the amount of beats per minute of neonatal rat cardiomyocytes similar to that seen with Angiotensin II (ANGII), which could be attenuated with losartan, an AT1 receptor blocker.<sup>4,5</sup> After several other experiments with the AT1-AA, they realized that the antibody had the same affinity and ability to activate the AT1 receptor as ANG II.<sup>4</sup> To understand the binding of the AT1-AA, they examined the number of beats per minute with the AT1-AA and small peptide sequences that corresponded to the AT1- receptor. From these experiments they identified a very specific seven amino acid (7AA) sequence on the 2<sup>nd</sup> extracellular loop of the receptor as the binding site of the AT1-AA. It is important to note that the AT1-AA does not compete for the AT1 receptor with ANG II, but rather the AT1-AA appears to enhance the binding and downstream effects of ANG II during pregnancy.<sup>6,9,10</sup> Rather not the AT1-AA enhances ANG II binding and signaling in the absence of pregnancy is unknown, and is warranted for future research.

### AT1-AA in Diseases

AT1-AAs are not only elevated in women with preeclampsia, but are also elevated in normotensive pregnancies with uterine growth-restricted fetuses, kidney transplant recipients undergoing renal rejection, patients with systemic sclerosis, vasculopathy, tissue fibrosis, hypertension, renovascular disease, and pregnant women with HELLP syndrome (a pregnancy disease characterized by Hemolysis, Elevated Liver enzymes, and Low Platelet count).<sup>12–16</sup> AT1-AAs appear elevated in women with PE and women with abnormal uterine perfusion pregnancies as early as the second trimester of pregnancy.<sup>17</sup> This suggests that AT1-AA may play a critical role in the pathogenesis of PE. Further studies by Hubel *et al*,

show that some postpartum preeclamptic women have increased circulating concentrations of AT1-AA more than one year after delivery.<sup>18</sup> The postpartum effects of AT1-AAAs infused into rats during pregnancy caused an increase in blood pressure, heart rate, decreased cardiac function, cellular hyperplasia, and increased in susceptibility to ischemia/reperfusion injury in rats 16 weeks postpartum.<sup>19,20</sup> Furthermore, not only were pregnant rats effected postpartum, but also the rat's fetuses, which exhibited an increase in apoptosis of myocardial cells and susceptibility to ischemia-reperfusion injury.<sup>19,20</sup> In women, it is known that preeclamptic women are at a 5–12 fold risk of end-stage renal disease, 2 fold risk of stroke, and 2 fold risk of cardiovascular disease later in life.<sup>21–24</sup> Therefore it is possible that the sustained level of AT1-AAAs in PE women, which first appeared during their PE episode during pregnancy, could be a risk factor for the development of cardiovascular disease, renal disease, and stroke for women later in life.

### AT1-AA Induced hypertension- a model for PE

AT1-AAAs cause an increase in blood pressure as well as other factors associated with PE, thereby making AT1-AAAs administered to rats a model of PE. This model can be referred to as the AT1-AA induced hypertensive model in pregnant rats. One of the more prevalent current models of PE is the reduced uterine perfusion pressure (RUPP) model. The major characteristics of this model are hypertension, intrauterine growth restriction, proteinuria, increase in inflammation, increase in oxidative stress, endothelial dysfunction, and an increase in sflt-1.<sup>25</sup> As shown in a study done by LaMarca *et al*, infusion of AT1-AA from serum of RUPP rats into pregnant rats increases blood pressure, as well as tissue concentrations of preproendothelin, a precursor for a vasoconstrictive factor ET-1, which is associated with late pregnancy PE.<sup>9,26,27</sup> Furthermore, there is significant evidence of endothelial dysfunction as a result of AT1- AA infusion.<sup>9,26,28,29</sup> AT1-AAAs increase production of reactive oxygen species causing oxidative stress in the placenta during pregnancy.<sup>8–10</sup> It is hypothesized that PE patients having increased AT1-AAAs and abnormal uterine Doppler ultrasounds, that AT1-AAAs can contribute to the impairment of placenta and fetal development due to increased placental vasoconstriction.<sup>17,30</sup> Not only is there a decrease in placental blood flow due to placental vasoconstriction, but also an increase in renal vascular resistance.<sup>10</sup> In our in-vivo and ex-vivo experiments, we have shown an increase in renal artery resistance index and vasoconstriction of isolated renal afferent arterioles from normal pregnant rats, incubated with the AT1-AAAs and further constricted with ANG II and the AT1-AA<sup>9</sup>. Studies conducted by Cunningham *et al*, demonstrated that the increase in renal vascular resistance (RVR) observed in ANG II and AT1-AA rats could be attributed to the systemic 3 fold increase in plasma isoprostane concentrations, a marker for oxidative stress.<sup>10</sup> Moreover, there is also evidence that AT1-AA causes increases in sFlt-1 which can in turn increase proteinuria and is a major cause of hypertension during pregnancy.<sup>31,32</sup> Tumor necrosis factor alpha (TNF- $\alpha$ ) is elevated in AT1-AA infused pregnant rats.<sup>31</sup> TNF- $\alpha$  is slightly elevated in a normal pregnancy, but is increased by twofold in preeclamptic pregnancies.<sup>33,34</sup> While it has recently been shown that TNF-  $\alpha$  is increased in pregnant mice with an injection of AT1-AAAs<sup>31</sup>, we have shown AT1-AA to be produced in response to TNF alpha induced hypertension during pregnancy. Moreover, multiple studies have shown that TNF-  $\alpha$  and AT1-AA contributes to increases in soluble

fms-like tyrosine kinase (sFlt-1) all of which are strongly implicated in the pathology of PE during pregnancy in the rat.<sup>31,32</sup>

It has been shown previously in our lab that infusion of AT1-AA causes increased placental oxidative stress<sup>9</sup> partly due to activation of NADPH oxidase, which produces superoxide.<sup>35,36</sup> Superoxide is a potent reactive oxygen species that is elevated in preeclamptic patients, where it can cause vascular dysfunction, poor invasion of trophoblast cells for placentation, placental hypoxia, release inflammatory cytokines, decrease nitric oxide bioavailability, and increase antiangiogenic factors, such as sFlt-1.<sup>37</sup> Administration of the antioxidant, tempol, attenuated the rise in hypertension in response to AT1-AA administered to pregnant rats along with decreasing the renal artery resistance index.<sup>8,9</sup> Therefore these studies suggest that oxidative stress is a major contributor to the pathology of hypertension due to AT1-AAs in PE. To understand the role of AT1-AA's activation of the AT1 receptor to increase oxidative stress and lead to hypertension; administration of losartan attenuated the increased oxidative stress and hypertension in AT1-AA induced hypertensive rats.<sup>8</sup> Thus supporting the link between AT1 receptor activation and increased oxidative stress.<sup>8,10</sup> Therefore blockade of AT1-AAs to improve blood pressure through a decrease in reactive oxygen species, such as superoxide, could be a potential therapy for PE patients.

### AT1-AA Renal Function

Studies from our lab have shown that AT1-AA alone decreases glomerular filtration rate (GFR), renal function, by decreasing renal blood flow (RBF) and renal vascular resistance (RVR) in pregnant rats.<sup>10</sup> These studies also show a greater and significant 3 fold increase in RVR with pregnant rats infused with both ANG II and AT1-AA together.<sup>9,10</sup> The increase in RVR caused a significant decrease in RBF and GFR in these studies.<sup>10</sup> Renal afferent arterioles from pregnant rats subjected to a dose of either ANG II or AT1-AA alone did not cause vasoconstriction, but with both ANG II and AT1-AA there was an increase in vasoconstriction.<sup>10</sup> Therefore these data taken together suggest a synergistic effect with ANG II and the AT1-AA especially in the kidney and suggest that AT1-AAs in pregnancy enhance ANG II mediated RVR, which leads to a decrease in renal function.

### AT1-AA Endothelial Function

One pathway by which AT1-AAs increase blood pressure is by activating the endothelin-1(ET-1) system. In a previous study from our lab, we found that AT1-AA treated rats had an increase in blood pressure and preproendothelin (PPET-1) mRNA expression in the placenta, kidney, and the aorta.<sup>9,26,36</sup> This increase in blood pressure was eliminated with the infusion of ET<sub>A</sub> receptor antagonist. In a more recent study it was demonstrated that AT1-AA and ANG II both stimulate endothelial cells to secrete ET-1, and that a combination of the two increases the secretion to greater magnitude.<sup>38</sup> Furthermore we have shown that PPET-1 mRNA was blunted in AT1-AA induced hypertensive rats with AT1 receptor antagonist.<sup>26</sup> PPET-1 is increased in the renal cortices and placentas of rats with an infusion of both ANG II and AT1-AA. (Brewer et al.).<sup>9</sup> Furthermore, studies by Roberts *et al*, showed that human umbilical vein endothelial cells (HUVECs) incubated with the serum from RUPP rats had a 2 fold increase in ET-1 production after 6 hours of exposure.<sup>39</sup> They

also showed that HUVECs incubated with RUPP serum had a 3 fold increase in ET-1 after 18 hours of exposure with RUPP serum.<sup>39</sup> Thus these results taken together suggest that circulating factors in the RUPP serum causes an increase in ET-1.<sup>39</sup> HUVECS cells treated with RUPP serum and pretreated with losartan, an AT-1 receptor antagonist, ET-1 production was normalized to concentrations of HUVECS incubated with normal pregnant rat serum.<sup>39</sup>

## AT1-AA future directions and therapy

It has been shown that inhibition of the AT1 receptor by angiotensin II receptor blockers (ARB), improves blood pressure, renal function, and circulating sFlt-1.<sup>40–42</sup> However ARBs are not good during pregnancy due to their well-documented association with birth defects.<sup>43–46</sup> Thus another therapeutic option to inhibit the actions of AT1-AAs directly is warranted. Recently, we have shown that AT1-AA inhibition by a specific modified peptide sequence which binds AT1-AAs and prevent them from binding to the AT1 receptor during pregnancy improved the PE symptoms associated with placental ischemic rats. Specifically, we showed improvement in maternal blood pressure, secretion of anti-angiogenic and vasoconstrictive factors (such as pre- proendothelin, sFlt-1), renal function, systemic NO bioavailability, and oxidative stress in RUPP (rat model of PE) rats. We also showed a decrease in cytolytic natural killer cells, which are associated with PE in women and mediators of oxidative stress and secrete inflammatory cytokines that can cause tissue damage.<sup>47</sup> Our data did not show any improvements in birth weight from placental ischemic pregnant rats, but also did not show a further decline in pup weight, suggesting that AT1-AA inhibition is not toxic to the offspring.

## Summary

Understanding the role of the AT1-AA in the pathophysiology of preeclampsia is important, because it's evident that the AT1-AA plays a critical role in the pathophysiology of this disease and that it could be a potential therapeutic target (Figure 1). The studies collected in this review highlight the roles that the autoantibody to increase several factors associated with PE that can lead to hypertension. In conclusion we believe that blocking the autoantibody could serve as a major treatment for the disease and should be further explored.

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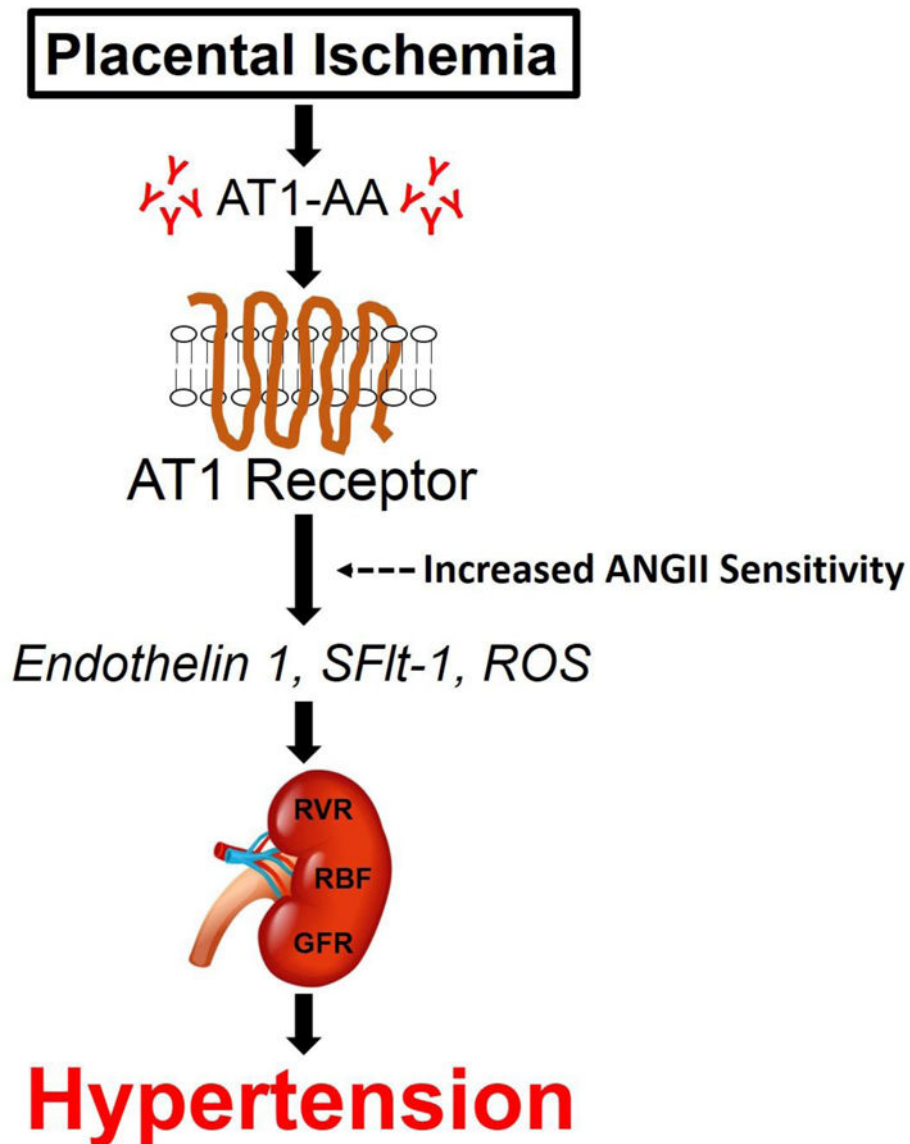
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**Figure 1. AT1-AA induced hypertension flowchart.**

In hypertensive pregnancies, placental ischemia occurs, which increases the production of AT1-AAs. AT1-AAs bind and activate g-coupled AT1 receptors to increase ANGII sensitivity and to stimulate downstream pathways to elevate circulating concentrations endothelin 1, sFlt-1, and ROS that have a pathological effect on the kidney to increase RVR, decrease RBF, and thus decrease GFR (i.e. renal function). Thereby these changes in circulating factors and renal function contribute to hypertension.

**Abbreviations:** AT1-AA, angiotensin II type I receptor antibodies; ANGII, angiotensin II; AT1, angiotensin II type I receptor; sFlt-1, fms-like tyrosine kinase-1; ROS, reactive oxygen species; RVR, renal vascular resistance; RBF, renal blood flow; GFR, glomerular filtration rate.