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Renin Angiotensin Signaling in Normal Pregnancy and Preeclampsia

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Summary

Many reports indicate that there is an increase in almost all of the components of the renin-angiotensin system (RAS) during an uncomplicated pregnancy, but renin activity, angiotensin II, and aldosterone decrease in preeclampsia (PE) for reasons that are unclear. PE is a life-threatening disorder of late pregnancy characterized by hypertension, proteinuria, increased soluble fms-like tyrosine kinase-1, as well as renal and placental morphologic abnormalities. Although a leading cause of maternal and perinatal morbidity and mortality, the pathogenic mechanisms of PE remain largely undefined. Immunologic mechanisms and aberrations of the RAS have been long considered contributors to the disorder. Bridging these two concepts, numerous studies report the presence of the angiotensin II type I receptor agonistic autoantibody (AT_1-AA) found circulating in preeclamptic women. This autoantibody induces many key features of the disorder through AT_1 receptor signaling, and has been implicated in the pathogenesis of PE. Here we review the functions of the RAS during normal pregnancy and PE, and highlight the role of AT_1-AA in both animal models and in the human disorder.

Classically described in the kidney, the renin-angiotensin system (RAS) is a hormone signaling cascade that regulates blood pressure and systemic electrolyte and fluid balance. In response to decreased blood pressure and low circulating sodium chloride, angiotensinogen, an α-2-globulin protein produced constitutively by the liver, is cleaved by the enzyme renin, which is synthesized and released by juxtaglomerular cells of the afferent renal arterioles (Fig. 1). Renin is rapidly produced and released by the macula densa.[1] The cleavage of the 452–amino acid angiotensinogen by renin yields the 10–amino acid long peptide, angiotensin-I (ANG I), and is the rate-limiting step of the cascade. The biologically inactive ANG I then is cleaved by angiotensin-converting enzyme (ACE), made primarily in lung endothelium, to the biologically functional angiotensin-II (ANG II), the eight–amino acid long effector molecule of the RAS.

ANG II exerts its effects through two major angiotensin receptors: AT_1 and AT_2. These highly conserved seven-transmembrane G-protein–coupled receptors share a 34% sequence identity and have comparable affinities for ANG II.[2] The AT_1 receptor is the predominant angiotensin receptor and is responsible for the majority of ANG II signaling. Its expression is fairly ubiquitous, and it is found abundantly in the adult kidney and on the surface of many cell types including vascular smooth muscle cells, adrenal glands, and

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syncytiotrophoblasts. It is coupled to a G_q protein, whose stimulation results in increased intracellular calcium resulting in vasoconstriction, increased sympathetic activity, and sodium and water retention. The minor angiotensin receptor, AT_2, is not highly expressed in the adult but predominates during fetal development, with its expression decreasing throughout the neonatal period.[3] AT_1 is more abundant than AT_2 in the adult kidney.[2] Stimulation of the AT_2 receptor inhibits cell growth, increases apoptosis, causes vasodilation, and regulates fetal tissue development.[4]

In addition to the classic circulating RAS, there is extensive evidence indicating that local RAS are present in many organs, such as the heart, ovary, and placenta.[5,6] Although these local systems may contribute to RAS functions, they are not the focus of this review, which will concentrate on the overall systemic effects of the RAS during pregnancy.

UNCOMPLICATED PREGNANCIES REQUIRE REGULATION OF THE RAS

During an uncomplicated pregnancy, the RAS undergoes specific changes. The up-regulation of renin is the first change to occur, mainly owing to the extrarenal release locally by the ovaries and maternal decidua.[7] As it grows, the placenta produces estrogen, a steroid hormone vital to sustain pregnancy. Estrogen also increases angiotensinogen synthesis by the liver, leading to increased serum ANG II.[8] The only RAS component that is reported to decrease during normal pregnancy is ACE.[9–11] Table 1 compares serum RAS component levels between nonpregnant women and pregnant women with no complications.

Many physiologic changes occur in the cardiac and renal systems during gestation that facilitate the expanding needs of blood supply and nutrients. Interestingly, during normal pregnancy, blood pressure is often slightly decreased in the initial trimesters, returning to baseline by delivery.[12] This phenomenon is puzzling because ANG II levels are increased during gestation.[13] The historic study by Assali and Westersten[14] revealed that healthy pregnant women are refractory to the vasopressor effects of ANG II. In fact, pregnant women require twice as much ANG II by intravenous infusion as compared with their nonpregnant counterparts to achieve similar vasomotor responses.[14,15] Some believe that this decreased ANG II sensitivity is explained by the presence of increased progesterone and prostacyclins during pregnancy.[16] In addition, the AT_1 receptors are in a heterodimeric state in ANG II–sensitive conditions, whereas during an uncomplicated pregnancy they are monomeric and are inactivated by reactive oxygen species (ROS).[17] Taken together, these studies explain why a normotensive pregnant woman may be insensitive to ANG II stimulation.

A healthy placenta is a dynamic organ that undergoes many changes throughout gestation that are essential to maintain a normal pregnancy. Placental trophoblasts are AT_1-receptor–rich, making them responsive to changes in the RAS.[18] Several recent studies showed that AT_1-receptor signaling regulates several genes responsible for normal trophoblast invasion[19] (eg, plasminogen activator inhibitor-1 [PAI-I]) and angiogenesis[20–22] (soluble fms-like tyrosine receptor-1 [sFlt-1]; soluble endoglin). In addition, AT_1-receptor stimulation also results in nuclear factor-κ B and the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH)-oxidase synthesis by trophoblasts.[23] These RAS-related changes in the placenta appear necessary for an uncomplicated pregnancy. Through the evidence provided in human studies, it is clear that the RAS undergoes specific and necessary changes to sustain a healthy pregnancy.

DYSREGULATION OF THE RAS IN PREECLAMPTIC WOMEN

Preeclampsia (PE) is a disorder of pregnancy characterized by hypertension and proteinuria. This life-threatening condition affects approximately 7% of pregnancies and results in substantial maternal and neonatal morbidity and mortality, and is therefore a major health concern.[24] In its advanced and severe form, the clinical symptoms of PE may include cerebral edema, renal failure, and the hemolysis, elevated liver enzymes, and low platelets syndrome. Treatment for PE is hampered by the lack of understanding of its pathogenesis and, through 2009, there were no effective interventions for either treatment or prevention. The only cure for the disorder is delivery of the infant and placenta. Although the underlying pathogenic mechanisms of PE remain largely undetermined, uteroplacental ischemia and the subsequent release of soluble factors, such as sFlt-1, from the placenta into the maternal circulation are thought to contribute to the maternal syndrome.[25]

The regulation of the RAS in PE differs from that in healthy pregnancies. Although most circulating RAS components increase in an uncomplicated pregnancy, this is not the case in PE because preeclamptic women have lower circulating levels of RAS components than do their normotensive pregnant counterparts[13,26,27] (Table 1). Two exceptions to these decreases should be noted. First, ACE is reportedly lower in pregnant woman as compared with nonpregnant women, and Merrill et al[9,10] showed that ACE levels are approximately equal in normotensive and preeclamptic women. Second, ANG-(1–7), a vasodilator produced by several tissues such as kidney, heart, hypothalamus, and ovary, is decreased significantly in PE.[9] Its exact role in the RAS and the regulation of a healthy pregnancy remains undefined. Although it may act through its own receptor, ANG-(1–7) interacts primarily with AT_1 and AT_2 receptors.[28,29] Overall, the profile of RAS components in a preeclamptic woman differs greatly from that of a healthy pregnant woman.

As previously mentioned, women experiencing an uncomplicated pregnancy show a relative vascular insensitivity to ANG II. Preeclamptic women, however, show increased ANG II sensitivity in their adrenal cortex and vascular system.[16,30] This could be explained by the heterodimerization of the AT_1 receptor in PE, whereas in healthy pregnancies, the receptors are monomeric and can be inactivated by ROS, resulting in ANG II insensitivity.[17] In this respect, evidence from an animal model that may be relevant to PE shows the AT_1 receptor forms a heterodimer with the bradykinin receptor (B2)[17,31] and the ROS-inactivation resistant AT_1/B2 heterodimers are hyperresponsive to ANG II.[17,32,33] Future investigation into the heterodimeric receptors and PE is necessary. Although it is widely accepted that the RAS is dysregulated in the setting of PE, the triggering factor leading to this imbalance remains unidentified.

IN VIVO STUDIES OF THE RAS AND HYPERTENSIVE DISORDERS OF PREGNANCY

Animal models have contributed greatly to our understanding of the cellular interplay at the vascular level in women with PE because such models permit scrutiny of alterations in the RAS in multiple cell types. The use of rodent models is especially relevant because the RAS of rodents and human beings are remarkably similar. The mouse has two pharmacologically identical isotypes of the AT_1 receptor, AT_{1a} and AT_{1b}.34,35 Human beings have a single AT_1-receptor isotype. In general, both human beings and rodents show an up-regulation of RAS components in an uncomplicated pregnancy.[36] With the exception of a few isolated reports in primates, we could locate no reports of spontaneous development of PE in animals suitable for laboratory study. However, through genetic and experimental manipulation, animal models with altered RAS have been developed and proven useful in delineating its role in both normal and abnormal pregnancies.

Both mouse and rat models have been used to investigate the changes in the RAS during pregnancy. When transgenic female mice expressing human angiotensinogen were mated with male transgenics expressing the human renin gene, Takimoto et al[37] observed transient hypertension in the dams. The hypertension was maximal in late pregnancy and resolved post partum. These females also showed another preeclamptic feature, proteinuria, but other manifestations, such as glomerular damage, myocardial hypertrophy, as well as placental abnormalities were less akin to the human disorder. In another experiment by the same group, the role of angiotensin receptors in mice during pregnancy was investigated. Female AT_{1a}-receptor knockout mice expressing the human angiotensinogen gene were mated with male mice expressing the human renin gene. The dams remained at their baseline blood pressure level throughout pregnancy, and showed no preeclamptic-like symptoms, despite having intact AT_{1b} receptors.[38] These findings suggest the importance of the RAS in blood pressure changes during normal pregnancy.

This group also used their transgenic mouse model to determine the timing of renin release in pregnancy.[37] They found that human renin expression increased late in gestation and was detectable both in chorionic trophoblasts and the maternal circulation of the pregnant transgenic mice. Our group also investigated the timing of renin gene expression during pregnancy using two different mouse strains, ICR and C57Bl/6. ICR mice showed high levels of renin expression at the maternal-fetal interface.[36] In C57Bl/6 pregnant mice, little placental expression of renin was observed, however, the gene was up-regulated in kidneys. Both ICR and C57Bl/6 mice showed an increase in circulating maternal renin during gestation, however, the sites of renin production differed. These animal models highlight how the regulation of the RAS may play a role in maintaining a normal pregnancy.

Taken together, several animal models exploring RAS regulation in pregnancy suggest that alteration in the elements of the RAS may be involved in the pathogenesis of gestational hypertensive disorders.

A SOURCE OF EXCESS AT_1-RECEPTOR ACTIVATION: THE ANGIOTENSIN II TYPE I RECEPTOR AGONISTIC AUTOANTIBODY

Although the altered regulation of the RAS in PE is largely accepted, the reasons for these alterations are yet to be identified. Although ANG II levels are reportedly decreased in preeclamptic women as compared with normotensive pregnant women,[16,30] these patients show symptoms that could be attributed to excess AT_1-receptor activation, such as hypertension and renal dysfunction. Again, the exact cause of this excess activation remains elusive. However, the discovery by Wallukat et al[39] that preeclamptic women harbor an autoantibody that stimulates the AT_1 receptor may explain this puzzling feature. It is possible that through excess AT_1-receptor activation, the angiotensin II type I receptor agonistic autoantibody (AT_1-AA) could produce preeclamptic phenotype symptoms in pregnant women, suggesting an important role of AT_1-AAs in the PE syndrome. Many recent studies have shown that by activating AT_1 receptors on a variety of cell types, these autoantibodies could increase certain factors that lead to preeclamptic pathophysiology such as endothelial cell dysfunction and vascular damage.[25,40] Examples of the possible contributions of AT_1-AA in the pathogenesis of PE are reviewed here and summarized in Figure 2.

In Vitro Studies Linking AT_1-AA to the Maternal Syndrome of PE

The autoantibody may contribute to the maternal symptoms of PE in a variety of ways. First, it may induce the liberation of sFlt-1. This anti-angiogenic factor may play a role in preeclamptic features[41,42] by binding to free vascular endothelial growth factor and

placental growth factor and inhibiting their angiogenic actions.[43–45] This soluble factor is increased in both the circulation and the placentas of preeclamptic women[40,46–49] and may contribute to the maternal symptoms of PE by impairing angiogenesis, leading to placental and renal dysfunction. Maynard et al[48] infused adenoviruses containing RNA of sFlt-1 into pregnant rats resulting in high circulating levels of this antiangiogenic protein, which induced a preeclamptic-like state: increased blood pressure, proteinuria, and renal histopathologic changes similar to those observed in human beings, such as glomerular endotheliosis. The placenta also produces sFlt-1 through AT_1-receptor stimulation of trophoblast cells via the calcineurin-NFAT pathway even during normal gestation.[21] Zhou et al[20,21] reported that sFlt-1 secretion was induced by autoantibodies derived from preeclamptic patient sera in human placental explants and a human trophoblast cell line and that increased circulating sFlt-1 levels are observed in AT_1-AA–injected pregnant mice.[50] Taken together, these findings suggest that the autoantibody, through AT_1-receptor activation, can additively contribute to the excess sFlt-1 secretion reported in preeclamptic patients.

Excess AT_1-receptor activation also may lead to increased PAI-1 in preeclamptic women. PAI-1 is a serine protease and is increased in PE.[51,52] Excess PAI-1 could lead to shallow trophoblast invasion, a hallmark of preeclamptic placentas. Studies have shown that by activating trophoblastic AT_1 receptors, AT_1-AA increases PAI-1 levels19,53 and decreases trophoblast invasion in vitro.[19,54] In the kidney, ANG II partially controls mesangial cell PAI-1 production.[55,56] In vitro experiments by Bobst et al[19] revealed that AT_1-AAs, through AT_1-receptor activation on cultured human mesangial cells, increase PAI-1 secretion. The accumulation of PAI-1 could result in decreased extracellular matrix degradation and subendothelial and subepithelial fibrin deposits, thereby contributing to kidney damage.[57,58] Excess glomerular fibrin deposition decreases the kidney's filtration ability.[59,60] Therefore, by overstimulating the RAS, AT_1-AAs increase PAI-1 in both the placenta and kidney and lead to decreased fibrinolysis and extracellular matrix breakdown, which could contribute to the organ damage and symptoms associated with PE.

The autoantibody may induce the production of other factors associated with PE such as ROS, NADPH oxidase, intracellular calcium, and tissue factor (TF). In PE, the generation of ROS is increased and may contribute to end-organ damage.[61] This excess ROS production may be via AT_1-receptor–mediated up-regulation of NADPH oxidase and nuclear factor-κ B. Dechend et al[23] confirmed that NADPH oxidases are increased in preeclamptic placentas and that the autoantibody increases ROS through this mechanism in vascular smooth muscle cells, placental trophoblasts, as well as in and around placental blood vessels. Also increased is the intracellular calcium level in erythrocytes, lymphocytes, and platelets of preeclamptic women.[62–65] Thway et al[66] investigated the possible role of AT_1-AA in the increase of free intracellular calcium. This group found that IgG isolated from preeclamptic patients was capable of activating AT_1 receptors and increasing intracellular calcium, whereas IgG derived from normotensive pregnant women could not. The increased intracellular Ca^{2+} resulted in the activation of the NFAT transcription factor.[66] This suggests that AT_1-AA may contribute to increased calcium in the cell, which regulates the downstream signaling pathways associated with PE. Also increased in PE is TF, the initiating protein of the extrinsic path of coagulation.[51] Excess TF may induce vascular damage resulting in the state of hypercoaguability, and, rarely, disseminated intravascular coagulation, experienced in some severely preeclamptic patients. AT_1-receptor activation, via AT_1-AA, has been shown to increase TF expression in vascular smooth muscle cells[67] and monocytes,[68] which may contribute to the hypercoaguability associated with PE. Taken together, these facts implicate that excess AT_1-receptor activation by the autoantibody may contribute to the maternal features of PE (Fig. 2), suggesting an important role of AT_1-AA in the pathogenesis of the disorder.

ANIMAL MODELS AND THE ROLE OF AT_1-AA IN THE MATERNAL AND FETAL FEATURES OF PE

Most of the evidence presented earlier was performed in vitro. To fully understand the role and pathogenic capabilities of the autoantibody, in vivo animal studies must be performed. Described here are the animal models that show the possible contributions and relationships of AT_1-AA to both the maternal and fetal features observed in PE.

Animal Models Elucidating the Role of AT_1-AA and Maternal Features of PE

To investigate the role of AT_1-AA in the development of gestational hypertension, Dechend et al[69] mated female rats expressing the human angiotensinogen gene with male transgenic rats expressing the human renin gene. Toward the end of their pregnancy, these dams experienced hypertension and proteinuria that resolved post partum. These females developed other preeclamptic-like features, such as glomerular fibrin deposition and placental vascular defects. Importantly, the same autoantibody circulating in preeclamptic women, AT_1-AA, was detectable in the serum of these pregnant transgenic rats.[69] The remarkable finding of AT_1-AA production in the setting of RAS dysregulation implies that these features may have a close relationship in the pathophysiology of PE.

Another group used a model of placental ischemia to understand the pathophysiology of PE. Granger et al[70] performed the surgical manipulation of reduction in uterine perfusion pressure in rats to determine if this reduced placental blood flow could result in preeclamptic features. Indeed, the reduction in uterine perfusion pressure–treated rats experienced preeclamptic-like features: hypertension, proteinuria, and increased sFlt-1, tumor necrosis factor (TNF)-α, endothelin production, and endothelial dysfunction. Also, AT_1-AA could be isolated from the manipulated rats, whereas unmanipulated pregnant rats did not produce the autoantibody.[71] The same group investigated the effect of TNF-α during pregnancy. Again, hypertension developed and AT_1-AA was detectable in the circulation of pregnant rats infused with low-dose TNF-α throughout pregnancy.[71] Nonpregnant animals did not share similar features, implying that adequate placental perfusion is necessary for a healthy pregnancy, and that decreased perfusion may lead to an inflammatory response triggering autoantibody production. The development of AT_1-AA in both reduction in uterine perfusion pressure and low-dose TNF-α–treated rats suggests an important relationship between RAS regulation and maternal health during pregnancy.

To definitively show this autoantibody is a causative agent in PE, Zhou et al[50] injected AT_1-AA purified from preeclamptic women into pregnant mice. The pregnant mice adoptively transferred with the autoantibody showed the key maternal features of the disorder: hypertension, proteinuria, and increased circulating sFlt-1. Human IgG derived from normotensive women undergoing uncomplicated pregnancies did not induce any preeclamptic features when injected into pregnant mice. To show specificity to the autoantibody, a short antibody-neutralizing epitope peptide was co-injected into some animals, which decreased autoantibody-mediated effects.[50] Losartan, an AT_1-receptor blocker, also attenuated AT_1-AA–-induced features. These studies suggest that the autoantibody found in preeclamptic women may contribute to the pathophysiology of the disease through excessive AT_1-receptor activation.

The animal models presented here relating the autoantibody to PE provide substantial evidence of the close relationship between alterations in the physiologic adaptations of the RAS in pregnancy, AT_1-AA, and maternal symptoms.

Animal Models Exploring the Role of the RAS and AT_1-AA in the Fetal Features of PE

PE has adverse effects on the fetus as well as the mother. Placental dysfunction leading to preterm birth and intrauterine growth restriction (IUGR) commonly are observed in PE.[72,73] The RAS regulates many components that could contribute to these features. For example, ANG II decreases system A amino acid transporter activity in the placenta through AT_1-receptor activation, which may contribute to IUGR.18 The RAS also plays a critical regulatory role in fetoplacental gene expression and circulation, which regulates fetal oxygenation, maturation, and health. In a double AT_1-receptor knockout mouse model it was shown that AT_1 receptors are essential to achieve appropriate somatic growth and maintenance of normal kidney structure.[74] Expanding on the work of Takimoto et al,[37] both and Saito et al[38] and Furuya et al[75] found that pups born to female transgenic mice expressing human angiotensinogen who mated with males expressing human renin displayed characteristics of IUGR. The newborns were small with undersized thoracic and visceral organs, suggesting that overexpression of RAS components may regulate fetal growth. These many examples suggest how alterations in the RAS may contribute to IUGR in the setting of PE.

In this regard, the autoantibody, through excess AT_1-receptor activation, also may alter normal RAS functioning in the developing fetus. Therefore, Irani et al[76] examined the fetuses of AT_1-AA adoptively transferred pregnant mice. The fetuses of AT_1-AA–injected dams were small and showed evidence of delayed organ maturation in the kidneys and liver, as compared with pups born to mice injected with IgG derived from normotensive pregnant women. Although the significance of these findings still must be explored, their observation highlights a possible role of the autoantibody and AT_1-receptor signaling in normal fetal development.

AT_1-AA: PREVALENCE, PERSISTENCE, AND THE PUSH FORWARD

The exact etiology of self-recognizing antibodies in autoimmune diseases is difficult to discern. Many factors have been proposed that may lead to autoantibody production in general, including genetic predispositions, maladaptive immune responses, and environmental triggers.[77–79] All of these mechanisms could contribute to the generation of the autoantibody associated with PE. It is currently unknown what triggers the production of AT_1-AA and when the autoantibody first arises in pregnancy. In their original article, Wallukat et al[39] used affinity purification and peptide competition experiments to illustrate that the autoantibodies found circulating in preeclamptic women have a common epitope: a seven–amino acid sequence on the second extracellular loop of the AT_1 receptor. In another human study, Siddiqui et al[80] showed more than 95% of 37 preeclamptic women harbored AT_1-AA and that the bioactivity of the autoantibody correlated significantly to disease severity, in particular proteinuria. Normotensive pregnant women also were assessed for the presence of AT_1-AA. Less than 30% of these women had any detectable autoantibody levels, which were five-fold less than those observed in the preeclamptic group. The consistencies of these studies suggest a common immunologic origin of AT_1-AA in preeclamptic women, an area of exciting future work.

Preeclamptic symptoms usually abate within 48 hours postpartum and normal blood pressure is restored approximately 12 weeks after delivery. However, a definitive timeline of AT_1-AA persistence in preeclamptic women is currently unknown. In a small study, Hubel et al[81] reported that 17.2% of 29 women with a previous history of preeclampsia harbored AT_1-AA 18 ± 9 months post partum, versus 2.9% of 35 women without a previous history of the disorder. Future work will have to build on this study to determine exactly when autoantibody titers decrease post partum in preeclamptic women.

The long-term cardiovascular and renal consequences of PE are areas of recent interest. Many groups have reported that having a previous history of PE puts a woman at increased risk for overall cardiovascular risk,[82] stroke and chronic hypertension later in life,[83,84] ischemic heart disease,[85] and death owing to cardiovascular complications,[86] as compared with women who have not suffered from the disorder. Renal complications also may persist in preeclamptic women. Glomerular endothelial cell swelling with fibrin deposition,[87] microalbuminuria, and endothelial cell dysfunction[88,89] all have been documented in preeclamptic women several months post partum. It will be of particular interest to determine if AT_1-AA are present in the women with a history of PE who go on to suffer from cardiovascular and renal complications later in life.

Taken together, the common immunologic features and long-term sequelae in these human studies provide mounting evidence that PE may in fact be an autoimmune disorder of pregnancy. Should this be the case, autoantibody-targeted therapies may be beneficial in the limited treatment of this prevalent and devastating disease of mother and child. Future investigation into the natural history of these autoantibodies in preeclamptic women is necessary.

CONCLUSIONS AND SIGNIFICANCE

The RAS is altered in gestation, suggesting a crucial role in maintaining a normal pregnancy. It also is possible that failure to achieve the adaptations seen in an uncomplicated gestation contributes to the pathophysiology of PE. Although the RAS is generally up-regulated in an uncomplicated, normotensive pregnancy, this balance is lost in PE. The exact cause of this disequilibrium remains undetermined and requires further investigation.

One possible contributor to the aberrant RAS in PE is the autoantibody, AT_1-AA. By increasing AT_1-receptor signaling, it acts as ANG II to enhance the RAS cascade without increases in other RAS components. Its AT_1-receptor agonistic capabilities have been reported in several in vivo and in vitro models to be associated or evoke the maternal features of PE, such as inducing hypertension and proteinuria, as well as sFlt-1 secretion. AT_1-AAs also have been shown to contribute to fetal injury in an adoptive transfer mouse model. Moreover, autoantibody effects can be specifically blocked by losartan, an AT_1-receptor antagonist and by a 7-aa peptide, which is the epitope of the autoantibody and corresponds to a sequence on the second extracellular loop of the AT_1 receptor. The consistency of this epitope suggests a common immunologic origin of the AT_1-AAs and implies that PE may be an autoimmune disease.

These facts have significant therapeutic implications in the management of PE. As evidence of AT_1-AA as a cause for human PE are validated, studies designed using the specific neutralization of the autoantibody in preeclamptic women could improve on its current treatment. The latter is now quite limited to ending the pregnancy, often prematurely. Should physicians be able to identify the autoantibody early in pregnancy and then block autoantibody-mediated AT_1-receptor activation, preeclamptic symptoms may be forestalled or prevented, reducing the risks to preeclamptic mothers and their unborn children.

Abbreviations

ANG II	angiotensin II
AT_1-AA	angiotensin II type I receptor agonistic autoantibody
NT	normotensive

PE	preeclampsia
sFlt-1	soluble fms-like tyrosine kinase-1
RAS	renin-angiotensin system

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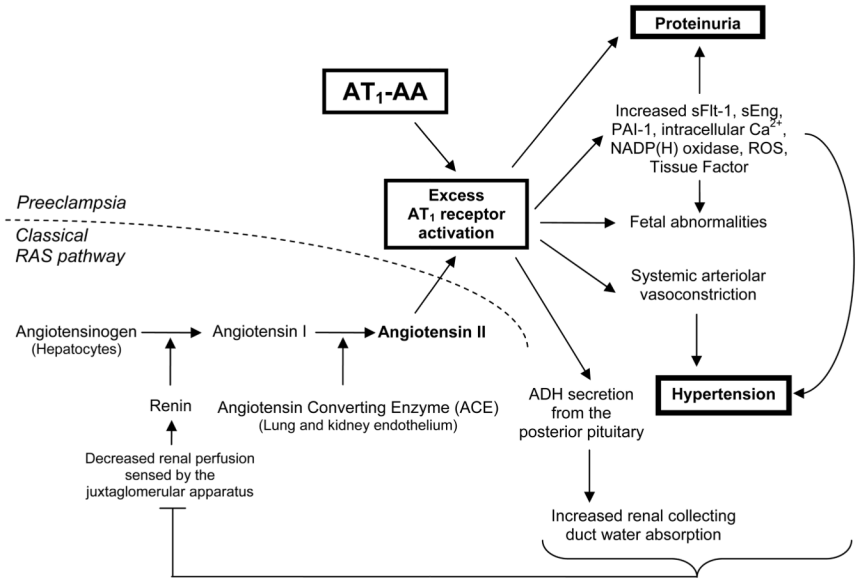

Figure 1.

The RAS cascade and PE. Although its end-effects are increased, ANG II, the key effector molecule of the RAS, is not up-regulated in PE. The autoantibody, AT_1-AA, through AT_1-receptor activation, may lead to the maternal features, such as vasoconstriction and increased blood pressure, observed in the disease. ADH, antidiuretic hormone; sEng, soluble endoglin.

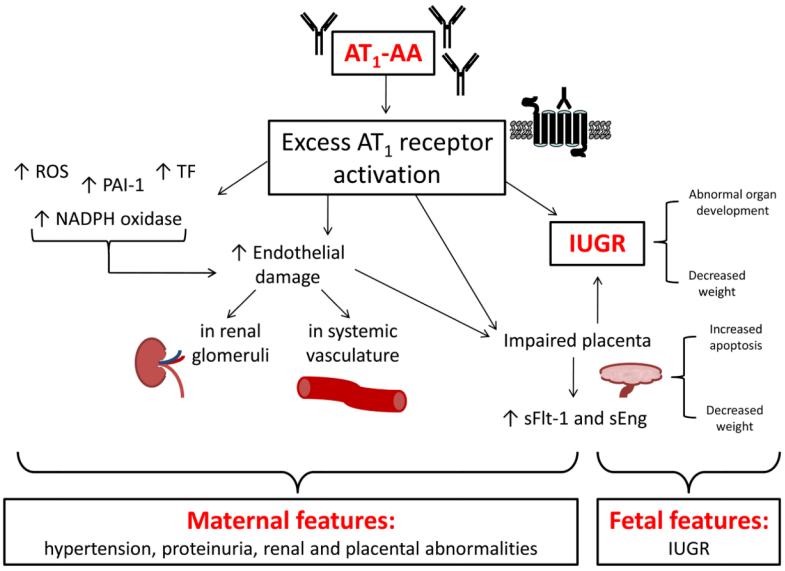

Figure 2.

The role of the autoantibody in the maternal and fetal features of PE. The autoantibody, AT_1-AA, through excess AT_1-receptor activation, may contribute to both the maternal and fetal features observed in PE. sEng, soluble endoglin.

Table 1

Comparison of Circulating Molecules in Normotensive and Preeclamptic Pregnancies Versus Nonpregnant Women

Serum RAS Component	Normotensive Pregnancy	Preeclamptic Pregnancy	Studies
Renin	++	+	Hsueh et al,[7] Langer et al[13]
ANG I	++	+	Merrill et al,[9] Langer et al[13]
ACE	-	-	Merrill et al,[9] Oats et al,[10,11] Langer et al[13]
Aldosterone	++	+	Brown et al,[27] Langer et al[13]
ANG-(1–7)	++	-	Merrill et al[9]
ANG II	++	+	Langer et al[13]
ANG II sensitivity	Refractory	Sensitive	Gant et al,[16] Abdul-Karim[15]
AT_1-AA presence	<30%	>90%	Wallukat et al,[39] Siddiqui et al[80]
AT_1-AA bioactivity	Low	High	Siddiqui et al[80]
AT_1 receptor	+, homodimer	++, heterodimer	Herse et al,[90] AbdAlla et al[17]
Molecules under partial AT_1r regulation			
sFlt-1	++	+++	Maynard et al,[48] Levine et al,[42] Zhou et al[21,50]
sEng	++	+++	Venkatesha et al,[91] Zhou et al[22,50]
PAI-1	+	++	Estelles et al,[51] Shaarawy and Didy,[92] Bobst et al[19]
Tissue Factor	+	++	Estelles et al,[51] Dechend et al[67]
NADPH oxidase, ROS	+	++	Hubel,[61] Dechend et al[23]

++, greatly increased over nonpregnant; +, slightly increased over nonpregnant; -, decreased compared with nonpregnant.

sEng, soluble endoglin.