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Role of angiotensin II type I receptor agonistic autoantibodies (AT1-AA) in preeclampsia

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Abstract

Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia are unclear. One important initiating event in preeclampsia is thought to be reduced placental perfusion leading to the production of a variety of factors that cause widespread dysfunction of the maternal vasculature. The major objective of this review is to discuss the potential role of a novel agonistic autoantibody to the angiotensin II type I receptor (AT1-AA) in mediating hypertension during pregnancy. Although animal studies suggest that increasing plasma AT1-AA concentration in pregnant rats to levels observed in preeclamptic women or placental ischemic rats result in significant increases in arterial pressure, the quantitative importance of AT1-AA in the pathophysiology of preeclampsia in humans has yet to be fully elucidated.

Introduction

Preeclampsia is estimated to affect 5-7% of all pregnancies in the U.S. (1-4). Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia are unclear. Hypertension associated with preeclampsia develops during the third trimester of pregnancy and remits after delivery, implicating the placenta as a central culprit in the disease. One important initiating event in preeclampsia is thought to be reduced placental perfusion leading to the production of a variety of factors that cause widespread dysfunction of the maternal vasculature (1-4). The major objective of this review is to discuss the potential role of a novel agonistic autoantibody to the angiotensin II type I receptor (AT1-AA) in mediating hypertension during pregnancy.

Angiotensin II type 1 receptor agonistic autoantibodies are present in preeclamptic women

The renin-angiotensin system (RAS) plays an important role in normal pregnancy and in preeclampsia. Normal pregnancy is associated with increased activation of RAS components

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but reduced vascular responsiveness to angiotensin II (5-10). In contrast, women with preeclampsia, have suppressed angiotensinogen, plasma renin activity and angiotensin II, but markedly enhanced vascular responsiveness to angiotensin II. A number of recent studies have also indicated that women with preeclampsia produce a novel agonistic autoantibody to the angiotensin II type I receptor (10-13). Dechend and colleagues previously reported that sera from preeclamptic women contain an IgG (type 3) autoantibody that reacts with the AT1 receptor. The binding of the AT1-AA to the seven amino acid stretch of the second extracellular loop of the angiotensin II type 1 receptor stimulates a chronotropic response from rat neonatal cardiomyocytes which can be attenuated with administration of an AT1 receptor antagonist, which is the basis of the bioassay primarily used for the detection of the autoantibody (11,14).

A number of recent studies have demonstrated increased concentrations of AT1-AA in serum from women with preeclampsia compared to serum from women with normal pregnancies (11-18). AT1-AA was also detectable in women with a history of preeclampsia up to 18 months after delivery (14). While the importance of the AT-AA in these women is unclear, the AT1-AA could be involved in the increase risk for cardiovascular diseases in women with a history of preeclampsia.

While one study has reported that pregnant patients with abnormal uterine artery Doppler flows had increases in the AT1-AA, whether preeclampsia was present or not (19-22), the levels of AT1-AA observed in these patients may have not been enough to elicit a chronic blood pressure response. Interestingly, patients with malignant hypertension who experienced humoral kidney transplant rejection also have high circulating levels of the AT1-AA (23). Fu et al., found that 33% of patients with malignant secondary hypertension due to renovascular disease had increased AT1-AA, thus suggesting that the AT1-AA is not limited to only preeclampsia (24).

The AT1-AA has been purified and investigators have shown that AT1-AA signaling, via the AT1 receptor, results in a variety of physiological effects. AT1-AA induces signaling in vascular cells and trophoblasts including transcription factor activation. The signaling results in tumor necrosis factor alpha and reactive oxygen species generation, both of which have been implicated in preeclampsia (12-18). Although these novel findings implicate AT1-AA in the pathogenesis of hypertension during preeclampsia, the specific mechanisms that lead to excess production and the mechanisms where by AT1-AA increases blood pressure during pregnancy remain unclear.

Placental ischemia is an important stimulus for AT1-AA production

Utilizing the bioassay for AT1-AA described above, we recently determined that reductions in placental perfusion in pregnant rats had a profound effect on stimulating AT1-AA production (11,14,16-18). In contrast, the AT1-AA was not detected in normal pregnant rats (Figure 1). In addition, we have been able to suppress the production of AT1-AA in the reduced uterine perfusion pressure (RUPP) model of placental ischemia by administration of CD20 blockade which acts through B lymphocyte depletion and therefore suppressed secretion of antibody (25). AT1-AA suppression via B cell depletion results in a blunted blood pressure response to placental ischemia (25). Collectively, these novel findings suggest that a reduction in placental perfusion may be an important stimulus for AT1-AA production in preeclampsia (See Figure 2).

In addition to placental ischemia as a stimulus for the AT1-AA we have shown that elevations of tumor necrosis factor-alpha (TNF- α) are also associated with increased production of the AT1-AA (26). Moreover, we have shown that chronic infusion of TNF- α in pregnant rats results in AT1-AA production. This would suggest the immune mechanisms

stimulated in response to placental ischemia may play an important role in AT1-AA production (see Figure 2).

Antigenic stimuli for the production AT1-AA are still unknown

The specific stimulus for the production of the AT1-AA during preeclampsia remains unknown. While the AT1-AA is implicated in preeclampsia and animal models of preeclampsia, it has also been found in other pathophysiological disorders such as patients with abnormal uterine artery Doppler flow and malignant hypertensives that had humoral kidney transplant rejection (22-24). These data suggests that the AT1-AA is not limited to only preeclampsia but yet in none of these diseases has the antigenic stimulus for the AT1-AA been found.

Interestingly, a recent study by Herse and colleagues found that the protein alignment of the binding site for AT1-to be highly homologous to the capsid protein VP2 of parvovirus B19 (27). Parvovirus B19 is a single-stranded DNA virus known to cause *erythema infectiosum*, mild childhood exanthema, having a seroprevalence of 80% in the general population. Many viral infections including Parvovirus B19 infection are implicated in various autoimmune diseases (28). Molecular mimicry to parvovirus B19 proteins can contribute to the appearance of autoimmune antibodies, such as antiphospholipid and antineutrophil cytoplasmic antibodies (28). The IgG against parvovirus B19 VP2-protein showed a positive reaction in the AT1-AA bioassay, which was blocked by an AT1 receptor blocker, as well as by the seven amino acid epitope binding sequence (27). Herse et al performed a prospective, nested, case-control study of 30 gestational age-matched women with preeclampsia and 30 normotensive pregnant women in which they measured AT1-AA and serum IgG against parvovirus B19 proteins (27). AT1-AAs were present in 70% of preeclamptic patients but absent in 80% of control subjects. The authors detected significantly more AT1-AA in women with an immune response corresponding with parvovirus B19 infection. Therefore they concluded that the presence of B19-specific antibodies directed against VP2 epitopes could play an important role in the molecular mimicry for the generation of AT1-AAs.

Moreover, we are now learning of the characteristics shared between preeclamptic women with autoimmune patients. For example the autoimmune associated T helper 17 lymphocyte has recently found to be elevated in the plasma of preeclamptic women (29). Further evidence implicates an imbalance between regulatory (Treg) and effector T cells, subclasses of CD4⁺ T lymphocytes, in preeclamptic women (29-31). Th17 secrete Interleukin 17, and play an important role in the development and progression of chronic inflammatory and autoimmune diseases such as lupus, allograft rejection, autoimmune arthritis, psoriasis and multiple sclerosis (32,33). Interleukin 17 induces the synthesis of other cytokines such as IL-6, granulocyte colony stimulating factor, TNF alpha, IL-8 and macrophage colony stimulating factor, all of which are associated with preeclampsia and we have previously shown to be associated with hypertension in response to reductions in uterine placental perfusion in pregnant rats (34-36).

The importance of AT1-AA in causing hypertension in response to placental ischemia

While the agonistic autoantibody to the Ang II type 1 receptor is elevated in preeclamptic women and in pregnant rats with reduced uterine perfusion or chronic elevations in circulating levels of TNF alpha, the importance of Ang II type 1 receptor activation in causing hypertension in preeclampsia or in RUPP or TNF alpha-induced hypertension in pregnant rats has yet to be fully elucidated. However, we recently reported that treatment with a selective angiotensin type 1 receptor antagonist, Losartan, markedly attenuated the

hypertension produced during placental ischemia as well as in response to chronic TNF excess in pregnant rats (16). Although these findings indicate that AT1 receptor activation plays an important role in mediating the increase in blood pressure in these animal models, our results do not quantify the relative importance of the AT1-AA in activating the AT1 receptor. It is important to note that a previous study from our laboratory indicated that chronic inhibition of endogenous angiotensin II formation, via oral administration of an converting enzyme inhibitor, decreased MAP to a similar extent in pregnant rats with reduced uterine perfusion pressure and normal pregnant rats. In addition, we also reported that plasma renin activity was not different between RUPP and normal pregnant rats. These data suggest that endogenous angiotensin II does not play a major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure in pregnant rats.

We also recently reported that infusion of purified rat AT1-AA, isolated from serum collected from a pregnant transgenic rat overproducing components of the renin angiotensin system, into pregnant rats from day 12 to day 19 of gestation, increased serum AT1-AA and blood pressure (17). Recent studies from Zhou et al also demonstrated that immunoglobulin isolated from preeclamptic women increases systolic pressure in pregnant mice (7,12,13). This phenotype was ameliorated with co-injection of an AT1 receptor antagonist or the 7 amino acid peptide that selectively blocks the actions of the AT1-AA. While these collective findings suggest that AT1-AA do have important hypertensive actions, the contribution of AT1-AA in the pathophysiology of hypertension in response to placental ischemia or preeclampsia remains to be an important area of investigation.

Mechanisms involved in AT1-AA induced hypertension during pregnancy

While the AT1-AA causes hypertension by direct activation of AT1 receptor, additional pathways involving endothelin and anti-angiogenic factors may also be involved during pregnancy (See Figure 1). We have recently reported that infusion of purified rat AT1-AA isolated from the transgenic rat model, (18) into normal pregnant rats increased serum AT1-AA, blood pressure, and tissue levels of preproendothelin (17). AT1-AA-induced hypertension in pregnant rats was attenuated by either oral administration of the AT1R antagonist losartan or an ET type A receptor antagonist. In addition, the increase in ET-1 transcript in response to AT1-AA induced hypertension was abolished by administration of an AT1R antagonist. These data suggest that AT1-AA induced hypertension during pregnancy is in part due to activation of the endothelin system.

We also recently reported that both circulating anti-angiogenic factors, sFlt-1 and sEng (sEng), are significantly elevated in AT1-AA-induced hypertensive pregnant rats(26). We examined the media of placental explants from AT1-AA induced hypertensive pregnant rats and found significant increases in sFlt-1, again indicating the placenta as a potential source of excess sFlt-1. However, when we examined soluble sEng from placental explant media, there was no difference when compared to the media collected from placentas of NP control rats, indicating that there is another cellular source for the sEng production. These data support the hypothesis that chronic immune activation in association with placental ischemia leads to sFlt-1 and sEng over expression via stimulation of the AT1-receptor possibly by production of the AT1-AA. These studies demonstrate an important interaction between inflammatory and angiogenic markers found to be produced excessively in response to placental ischemia.

Summary

Recent studies have demonstrated increased concentrations of AT1-AA in serum from women with preeclampsia compared to serum from women with normal pregnancies.

Results from animal studies indicate that placental ischemia may be an important stimulus for AT1-AA production during pregnancy. Generation of AT1-AA in response to reduced placental perfusion however may be secondary to inflammatory factors during preeclampsia. Several laboratories have demonstrated that chronic administration of AT1-AA in animal models elicits many of the phenotypic characteristic seen in preeclamptic women. In addition, suppression of AT1-AA production decreases blood pressure in response to placental ischemia in pregnant rats. These data suggest an important role for AT1-AA in the hypertension in response to placental ischemia.

Although animal studies suggest that increasing plasma AT1-AA concentration in pregnant rats to levels observed in preeclamptic women or placental ischemic rats result in significant increases in arterial pressure, the quantitative importance of AT1-AA in the pathophysiology of preeclampsia in humans has yet to be fully elucidated. Clinical studies utilizing specific antagonist of the AT1-AA or studies that block the formation of AT1-AA in preeclamptic women are the only approaches to truly determine the role of AT-AA in preeclampsia.

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Figure 1.

Top. Changes in mean arterial pressure (MAP) in response to placental ischemia in pregnant rats. Reduction in Uterine Perfusion (RUPP); Normal Pregnant (NP) rats. (* $P < 0.001$ vs control groups). All data are expressed as mean $\pm$ SEM.

Bottom. Angiotensin type 1 (AT1) autoantibodies in RUPP and normal pregnant (NP) rats as detected by the chronotropic responses (bpm) to AT1 receptor-mediated stimulation of cultured neonatal rat cardiomyocytes (* $P < 0.05$ vs NP rats; † $P < 0.05$ vs RUPP). All data are expressed as mean $\pm$ SEM.

Figure 2.

Hypertension in response to placental ischemia is associated with elevated proinflammatory cytokines, activated T and B lymphocytes and production of agonistic autoantibodies to the angiotensin II type I receptor (AT1-AA). AT1-AA stimulates the vasoconstrictor peptide (endothelin 1) and antiangiogenic peptide, soluble fms-like tyrosine kinase-1 (sFlt-1), to cause hypertension during pregnancy.