Editorial Comments

Pieces of the preeclampsia puzzle

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Introduction

Several interesting articles have been published recently that address novel mechanisms for preeclampsia. These mechanisms all involve circulating factors, a favourite topic for preeclampsia researchers. These factors may interfere with angiogenesis, engage angiotensin (Ang) II signalling, and directly impair endothelial function.

VEGF, PlGF and sFlt1

Vascular endothelial growth factor (VEGF) must be very busy during pregnancy. The growth factor’s receptor, fms-like tyrosine kinase 1 (Flt1), exists in two forms, namely a membrane-bound receptor tyrosine kinase that transmits angiogenic signals and a soluble secreted ectodomain (sFlt1), which may capture VEGF and keep the growth factor from its active bound receptor. Maynard et al. [1] found that sFlt1, a potential antagonist of VEGF and placental growth factor (PlGF), is upregulated in the placentas of preeclamptic women. This state-of-affairs led to increased systemic levels of sFlt1 in these women. The levels fell after delivery. Circulating sFlt1 in patients with preeclampsia was associated with decreased circulating levels of free VEGF and PlGF. Exogenous VEGF and PlGF reversed the resulting endothelial dysfunction in in vitro experiments. The authors then performed studies on rat renal arterioles and found that VEGF and PlGF both caused microvascular relaxation of rat renal arterioles. The relaxation was blocked by sFlt1. Finally, they showed that administration of sFlt1 to pregnant rats induces hypertension, proteinuria and glomerular endotheliosis. These are the classical lesions of preeclampsia. The observations of Maynard et al. [1] suggest that excess circulating sFlt1 contributes to the pathogenesis of preeclampsia. Thus, sFlt1 may be a preeclampsia factor [2].

During normal pregnancy, the uterine spiral arteries are infiltrated and remodelled by endovascular invasive trophoblasts, which increases blood flow appropriately to meet the oxygen requirements of the fetus. In the placenta of preeclamptic women, this trophoblastic invasion does not occur normally and therefore the blood flow is reduced. As a result, the placenta is ischaemic. Increased sFlt1 is produced, presumably as a response, which scavenges VEGF and PlGF thereby lowering circulating unbound VEGF and PlGF. The lowering of these vasodilatory growth factors contributes to endothelial dysfunction and multiorgan disease throughout the body. However, according to this scenario the trigger for ischaemia and hypoxia remains unknown. Whether sFlt1 is the trigger interfering with trophoblast invasion or whether sFlt1 secretion is solely the resulting mediator resulting from faulty trophoblast invasion remains unclear.

Agonistic antibodies against AT1 receptors

The second report was by Dechend et al. [3]. They continued their work on putative agonistic antibodies that stimulate the Ang II, AT1 receptor (AT1-AA). They performed an in vitro study and showed convincingly that these antibodies are capable of stimulating the NADPH oxidase in vascular smooth muscle cells and in isolated human trophoblasts. Furthermore, they found that NADPH oxidase is strongly activated in the placentas from preeclamptic patients. Furthermore, NF-κB was activated and IκBα reduced in placentas from preeclamptic women. The authors concluded that NADPH oxidase is potentially an important source of ROS that may upregulate NF-κB in preeclampsia. They suggest that AT1-AA through activation of NADPH oxidase could contribute to ROS production and inflammatory responses in preeclampsia. However, the mechanisms responsible for AT1-AA production

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are unknown. The putative antigen responsible for these antibodies is also unknown. The AT1 receptor could be an innocent bystander in this process.

**ADMA**

Another preeclampsia factor is asymmetric dimethylarginine (ADMA). Savvidou _et al._ [4] tested the hypothesis that ADMA, an endogenous endothelial nitric oxide synthase inhibitor, contributes to the development of preeclampsia. A role for NO, or its absence, has been established in earlier studies of preeclampsia. The authors measured forearm ischaemia reperfusion as a marker of endothelial function. They also monitored uterine blood flow by means of Doppler techniques. They searched for the occurrence of intrauterine growth retardation, and they obviously measured ADMA and its symmetrical analogue. The authors found that women with evidence for impaired placental perfusion had >30% prevalence of children with intrauterine growth retardation and >20% prevalence of preeclampsia. Women with preeclampsia clearly had significantly lower flow-mediated vasodilatation than women with normal uterine perfusion. In women with preeclampsia, there was a remarkably tight correlation between ADMA levels and flow-mediated vasodilatation. Taken together, the authors found that endothelial dysfunction develops before preeclampsia, women with higher uterine flow resistances are at risk for intrauterine growth retardation and preeclampsia, and ADMA may be a potentially contributing factor to endothelial dysfunction in these women.

**Possible interactions of apparently divergent pathways?**

Is it possible that these divergent mechanisms interact in some way? Ang II plays some role in angiogenesis. Angiotensin-converting enzyme inhibitors and AT1 receptor blockers appear anti-angiogenic and decrease microvessel formation [5]. VEGF-mediated angiogenesis can be decreased with AT1 receptor blockers [6]. ADMA generation can be diminished by ACE inhibitors and by AT1 receptor blockers in patients receiving these drugs [7]. How Ang II might stimulate ADMA formation is not clear. ADMA is synthesized from methylated arginine residues in proteins by protein arginine methyltransferases. The compound is metabolized to citruline by the actions of dimethylarginine dimethylaminohydrolases I and II. Could Ang II possibly play a role in upregulating sFlt1? The signal presumably has to do with hypoxia and therefore may involve the hypoxia-inducible factor HIF [2].

Interestingly, Ang II may increase HIF-1α induction. According to Page _et al._ [8], Ang II relies on ongoing translation to maintain elevated HIF-1α protein levels. Ang II increases HIF-1α translation by a reactive oxygen species (ROS)-dependent activation of the phosphatidylinositol 3-kinase pathway, which acts on the 5'-untranslated region of HIF-1α mRNA. Their results suggest that the non-hypoxic induction of the HIF-1α transcription factor via vasoactive hormones such as Ang II might be important for vascular biology.

**More questions than answers**

What upregulates Flt1 and what determines the relationship between the receptor forms? What is the relationship between Flt1 and Ang II if any? What is the antigen responsible for AT1-AA and do these antibodies really play a relevant role _in vivo_? What turns on ADMA production in pregnant women: could it be an Ang II related effect?

**Conflict of interest statement.** None declared.

**References**

1. Maynard SE, Min JY, Merchand J _et al._ Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. _J Clin Invest_ 2003; 111: 649-658
5. de Boer RA, Pinto YM, Suurmeijer AJ _et al._ Increased expression of cardiac angiotensin II type 1 (AT(1)) receptors decreases myocardial microvessel density after experimental myocardial infarction. _Cardiovasc Res_ 2003; 57: 434-442
7. Delles C, Schneider MP, John S, Gekle M, Schneider RE. Angiotensin converting enzyme inhibition and angiotensin II AT1-receptor blockade reduce the levels of asymmetrical N(G), N(G)-dimethylarginine in human essential hypertension. _Am J Hypertens_ 2002; 15: 590-593