From mother to child—transplacental effect of AT\textsubscript{1}R-AA in preeclampsia*

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Preeclampsia is a common hypertensive disorder of pregnancy and a leading cause of maternal and foetal morbidity and mortality worldwide. Preeclampsia requires the presence of the placenta and generally dramatically resolves after placental delivery. The abnormal placentation with failure of trophoblast remodelling of uterine spiral arteries represents a point where current theories on mechanisms responsible for the condition converge [1]. Various pathways have been proposed to contribute to placental disease. Two major recent concepts, namely, autoimmunity and anti-angiogenesis, have helped us gain new insights into this ‘disease of theories’. Possible mediators leading to impaired angiogenesis in the placenta were recently reviewed [2]. The autoimmunity notion received support with the discovery of autoantibodies directed against the angiotensin (Ang) II Type 1 receptor (AT\textsubscript{1}R-AA) in the serum of preeclamptic women [3]. AT\textsubscript{1}R-AA activate the AT\textsubscript{1}R and induce a cascade of events in various cell types, similar to the actions of Ang II [4]. Increased oxidative stress, increased production of soluble fms-like tyrosine kinase (sFlt-1) in the placenta and initiation of pro-inflammatory and pro-coagulation responses all appear to be key mechanisms resulting from AT\textsubscript{1}R-AA actions [5]. AT\textsubscript{1}R-AA were also found in a rodent model for preeclampsia. In that model, the dams of female rats transgenic for the human angiotensinogen gene developed severe (telemetry-measured) hypertension and albuminuria in the latter half of pregnancy, accompanied by glomerular endotheliosis [6]. Thus, many features of the preeclampsia-related maternal syndrome including hypertension, proteinuria and generalized endothelial dysfunction were attributed to circulating AT\textsubscript{1}R-AA. Preeclamptic AT\textsubscript{1}R-AA are IgG3 subclass immunoglobulins that target the structures contained in the second extracellular loop of AT\textsubscript{1}R and induce agonistic responses similar to Ang II despite a different binding site from the natural ligand [3]. Their actions can be neutralized with the corresponding seven-amino-acid peptide sequence or pharmacologic blockade of the AT\textsubscript{1}R.

Recent studies on the pathogenesis of preeclampsia focused mainly on the features of the maternal syndrome, as preeclampsia can lead to serious maternal and foetal complications. Agonistic antibody-mediated AT\textsubscript{1}R stimulation has been demonstrated in severe vascular renal allograft rejection and the passive transfer of human IgG containing AT\textsubscript{1}R-AA induced vascular lesions similar to the human disease. Furthermore, AT\textsubscript{1}R-AA led to increased blood pressure in otherwise non-rejecting and normotensive transplanted animals [7]. Investigators from the University of Texas in Houston pursued a similar strategy of passive human IgG transfer. They recently showed that AT\textsubscript{1}R-AA recovered from the circulation of women with preeclampsia induced preeclampsia-like generalized endothelial dysfunction in pregnant mice. Short duration (5 days) of the passive transfer induced an increase in tail-cuff blood pressure measurements. Links to impaired placental angiogenesis were demonstrated with an increase in sFlt concentrations in the serum of these pregnant mice [8]. sFlt is a shorter splice variant of the functional receptor that lacks the transmembrane domain. The shortened version interferes with angiogenesis and thereby placental development. Together with previous findings implicating overproduction of plasminogen activator inhibitor-1 and tissue factor in human trophoblast cells, their findings provided further evidence that AT\textsubscript{1}R-AA may have a causative role in abnormal placentation. Some prototypic features of maternal syndrome in terms of swelling of the endothelial cells (glomerular endotheliosis) were found in the antibody-transferred pregnant mice. However, the mouse model differed from the human disease. For instance, electron microscopic analysis revealed subendothelial deposits of immune complexes. Glomerular immune complex deposition is not common in human preeclampsia [9] and it remains to be determined whether or not the mice developed antibodies against human AT\textsubscript{1}R-AA IgG used in the transfer experiments.

The team from Houston now focused on foetal complications. Intrauterine growth restriction (IUGR) can be
found in about one-third of the babies born to preeclamptic mothers [10]. Structural abnormalities and impairment in placental perfusion are possibly responsible, yet these issues remain controversial. The placenta brings the maternal and foetal circulatory system into close proximity. This state of affairs facilitates the nutrient and gas exchange essential for foetal development. In their latest study [11], the Houston group used human AT\(_1\)R-AA-harbouring IgG that crossed the mouse placenta, entered foetal circulation and led to IUGR (Figure 1). The novel finding of the present study was that anti-angiogenesis-independent mechanisms were AT\(_1\)R-AA-mediated. The investigators observed apoptosis in human placental villous explants and in cultured human trophoblast cells exposed to the autoantibody [11]. The smaller, ‘under-perfused’ placentas could have contributed to impaired foetal organogenesis in the mouse offspring. The zone of nephrogenesis and the number of glomeruli were decreased in the kidneys of foetuses born to mice passively transferred with AT\(_1\)R-AA. This finding suggested that AT\(_1\)R-AA were responsible for the retarded renal development [11]. The livers of foetuses also showed developmental retardation. Both the pro-apoptotic effect \textit{in vitro} and impaired foetal growth and organogenesis were prevented by the blocking peptide directed against the antibody-binding site in this study [11]. According to the ‘Barker’ hypothesis, IUGR is associated with increased cardiovascular risk later in life [12,13]. As shown in Figure 1, maternal AT\(_1\)R-AA can cause both maternal and foetal pathology via pro-inflammatory, vasoconstrictive, pro-coagulatory and pro-apoptotic actions on the placenta. Whether or not AT\(_1\)R-AA may contribute to foetal pathology independent of placental effects is difficult to investigate. IUGR has also been observed in non-preeclamptic pregnancies.

Recent clinical data show that AT\(_1\)R-AA appear some weeks before the onset of the maternal syndrome and that the AT\(_1\)R-AA concentrations correlate with disease severity [14]. Timely detection and removal or inhibition of AT\(_1\)R-AA could have clinical utility in the medical management of preeclampsia. Moreover, treatment of the maternal condition could have a salubrious impact on long-term cardiovascular risk of both mother and child. Transplant recipients with severe vascular rejection due to AT\(_1\)R-AA stimulation benefited from extracorporeal antibody removal and pharmacologic receptor antagonists combined with intensified immunosuppression. However, AT\(_1\) receptor antagonists and ACE inhibitors cannot be used for treatment of women with preeclampsia because of teratogenicity [15,16]. AT\(_1\)R-AA removal with plasmapheresis or immunoadsorption would provide only short-term gains. Use of the peptide-binding sequence to inhibit AT\(_1\)R-AA would be difficult because of immunogenicity. Nevertheless, current data provide the platform for generation agents that could interfere with antibody binding to the target receptor. Novel treatments could be on the horizon; however, preeclampsia prevention programmes aimed at
alleviating poverty and malnutrition and controlling maternal obesity should also be implemented. A final nagging question remains that has yet to be experimentally answered. What is the mechanism leading to AT1R-AA production in preeclampsia and other syndromes?

References


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