

Aldosterone, Vascular Endothelial Growth Factor, and Preeclampsia
A Mystery Solved?

Christian Delles, Ellen Marie Freel

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom.

This paper was sent to S. Ananth Karamanchi. Guest editor, for review by expert referees, editorial decision, and final disposition.

Correspondence to Christian Delles, BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, 126 University Place, Glasgow G12 8TA, Scotland, United Kingdom. E-mail Christian.Delles@glasgow.ac.uk

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.111.00767

The renin–angiotensin system (RAS) is one of the key players in volume and sodium homeostasis. Activation of the RAS leads to vasoconstriction, sodium retention, and volume expansion via the action of angiotensin II and the effector hormone of the RAS, aldosterone. The RAS can also respond to changes in plasma volume; activation of the RAS is seen in states of volume contraction and will lead to restoration of plasma volume. Normal pregnancy is characterized by an increase in maternal plasma volume that is considered necessary for optimal perfusion of the placenta to meet the demands of the developing fetus. This volume expansion is mediated, at least in part, by activation of the maternal RAS with increased levels of renin, angiotensin II, and aldosterone in normotensive pregnant women.1

This view of the RAS in pregnancy is challenged by a number of observations. First, aldosterone levels are higher than expected from the levels of renin or angiotensin II.2 Additional stimulation of aldosterone secretion by factors other than angiotensin II has therefore been proposed. Second, activity of the RAS is not limited to the maternal kidneys and vasculature. Components of the RAS can be synthesized in the placenta, and local RAS activity can be found both in the maternal deciduas and in fetal tissues, including the spiral arteries.3 Third, the effects of an activated RAS in pregnancy are different from those in nongravid women. Most strikingly, normotensive pregnant women are refractory to the vasoconstrictor effect of angiotensin II,4 which may be one of the factors that explain a lower blood pressure than expected from the relatively high levels of angiotensin II. Through these adaptations of the RAS, the pregnant woman can benefit from its positive effects, in particular from volume expansion, regulation of trophoblast invasion, and angiogenesis. At the same time, the negative effects of the RAS, in particular vasoconstriction and hypertension, can be avoided.

Preeclampsia is a hypertensive disorder of pregnancy characterized by hypertension, proteinuria, and edema. It affects 2% to 8% of pregnancies and remains a major cause of maternal and fetal morbidity and mortality worldwide.5 The pathogenesis of preeclampsia is thought to be triggered by excessive maternal immune response to the developing trophoblast leading to placental oxidative stress, hypoperfusion, and hypoxia, and the subsequent release of placental factors causing widespread endothelial dysfunction in the maternal circulation. In turn, the resulting placental hypoperfusion is probably further aggravated by reduced activity of growth factors, including vascular endothelial growth factor (VEGF), placental growth factor, and transforming growth factor β1. Antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), a soluble form of the VEGF-1 receptor, and soluble endoglin, a part of the transforming growth factor β receptor, are released from apoptotic trophoblast cells and interact with and reduce the systemic and local levels of VEGF, placental growth factor, and transforming growth factor β1. Despite years of research into the condition, the pathogenesis of preeclampsia and the sequence of events remain incompletely understood.

Preeclampsia is characterized by relative intravascular volume depletion; it should therefore be associated with a compensatory activation of the RAS. This is not the case. On the contrary, aldosterone levels are lower in women with preeclampsia compared with those with normotensive pregnancies.6 It is unclear, however, whether failure of RAS activation and inappropriately low levels of aldosterone levels in pregnancy are a cause or simply a consequence of preeclampsia. In the current issue of Hypertension, Gennari-Moser et al7 present a comprehensive set of data that bring together the factors known to be involved in impaired angiogenesis with the failure of aldosterone to respond appropriately to volume contraction.

Gennari-Moser et al7 demonstrate that VEGF stimulates aldosterone synthesis in H295R adrenal cells as assessed by the conversion of 3H-deoxycorticosterone (DOC) to 3H-aldosterone. In addition to this direct effect of VEGF, the authors also observed an indirect effect in a model using endothelial cell–conditioned medium. Human umbilical vein endothelial cells were grown in medium optimized for endothelial cells; when this medium was transferred to H295R cells, it also stimulated aldosterone production pointing toward an endothelial cell–derived factor, and the effect was stronger when human umbilical vein endothelial cells were incubated with VEGF. Gennari-Moser et al7 did not measure VEGF concentrations in the endothelial cell–conditioned medium, but from their control experiment in human umbilical vein endothelial cells grown in medium...
optimized for adrenal cells that did not stimulate aldosterone production in H295R cells irrespective of incubation with or without VEGF, it can be concluded that the effects of preconditioned medium were dependent on factors released from endothelial cells. An effect of a potent growth factor, such as VEGF on adrenal cells and aldosterone production, is probably not surprising, but the magnitude of the effect definitely is. The authors show that the VEGF effect is more potent than, but also enhanced by, angiotensin II.

The major strength of the study by Gennari-Moser et al lies in the simplicity of the key message (that VEGF is a stimulator of aldosterone synthesis) combined with a series of elegant experiments to further dissect their findings. In detailed concentration–response experiments, using coinubcation of angiotensin II and VEGF, the authors show increasing CYP11B2 mRNA expression in H295R cells with increasing angiotensin II and VEGF concentrations; these findings are confirmed in subsequent Western blot experiments. Although the details of VEGF signaling in H295R cells remain unclear, Gennari-Moser et al demonstrate the presence of kinase insert domain receptor (Kdr, VEGF-2 receptor) but not Flt-1 (VEGF-1 receptor) in immunofluorescence experiments. They further show that VEGF more specifically stimulates aldosterone production than angiotensin II; although angiotensin II increased steroid hormone synthesis by inducing transcription of the steroidogenic acute regulatory protein, the authors found steroidogenic acute regulatory protein-independent increase in aldosterone production with VEGF. The in vitro data by Gennari-Moser et al are complemented by in vivo data in nonpregnant rats that were injected with adenoviruses expressing sFlt-1, a model that shows many preeclampsia phenotypes. These animals showed reduced capillary density in the zona glomerulosa compared with control virus–injected rats. In pregnant rats injected with adenovirus expressing sFlt-1, the authors observed an inverse correlation between serum sFlt-1 and aldosterone levels.

The studies by Gennari-Moser et al provide a mechanistic link between reduced VEGF and increased sFlt-1 levels (ie, antiangiogenic factors) and reduced aldosterone levels in preeclampsia. Not only would their data explain the inappropriately low-aldosterone levels in preeclampsia but also the higher than expected aldosterone levels in healthy pregnancy. The inhibitory effect of sFlt-1 on zona glomerulosa capillarization in their present study and previous data on the role of VEGF as tissue-specific angiogenic factor in adrenal cortex capillary endothelial cells fit nicely together.

Although the studies by Gennari-Moser et al provide important clues to solve the mystery of reduced aldosterone levels in preeclampsia, they leave us with a number of open questions. Crucially, the nature of the endothelial cell–derived factor present in endothelial cell conditioned medium remains unclear. Previous work provides evidence that it is not angiotensin II or endothelin, and there is reason to believe that it could be VEGF. Although not strictly necessary for the conclusions of the present study, data on VEGF concentration in supernatant of human umbilical vein endothelial cells grown in endothelial cell optimized and adrenal cell optimized medium would have further supported the conclusions. Also, the VEGF receptor studies in H295R cells and the zona glomerulosa capillary density data point toward signaling through VEGF-1 receptor (Flt-1), but in the end only selective inhibition or silencing of VEGF receptor subtypes will prove this point. Most importantly of course, although the study by Gennari-Moser et al used a range of different in vitro and in vivo models, the data will have to be confirmed in human tissues in normal and preeclamptic pregnancy. Some first evidence may be derived from studies looking at the relationships between circulating VEGF, sFlt-1, and aldosterone.

It is important to note that the study by Gennari-Moser et al may explain a key phenomenon in later stages of preeclampsia but does not provide immediate insights in the early triggers and early pathogenesis of the condition. The exact nature of the events leading to increased sFlt-1 levels in preeclampsia remains unclear; however, in addition to the well-known antiangiogenic effect of sFlt-1 that contributes to placental hypoperfusion and endothelial dysfunction, the authors now present convincing data that sFlt-1 also contributes to the paradoxically low aldosterone concentrations in preeclampsia.

There are other phenomena in the regulation of steroid biosynthesis in pregnancy that also require further studies. For example, during pregnancy, there is a significant increase in plasma progesterone (a key precursor in the synthesis of the mineralocorticoid hormone, DOC) concentration leading to a rise in circulating DOC levels from an average of 0.1 nmol/L to a peak of 1.5 to 10 nmol/L at the end of the third trimester, and DOC levels are even higher in pregnancies complicated by hypertension or preeclampsia. The plasma concentration of DOC during the third trimester of pregnancy is sufficient to cause hypertension in nonpregnant women, but despite this, hypertension occurs in only 5% to 8% of pregnancies. This discrepancy has led to speculation that the mineralocorticoid receptor may, in normal circumstances, be protected from activation by DOC by a prereceptor protective mechanism, the nature of which is unclear. Aldosterone is an important factor in the pathogenesis of hypertension and other cardiovascular traits, and a better understanding of the role of steroid hormones in pregnancy and their regulation may provide further insights in the pathogenesis of cardiovascular diseases. In fact, the increased cardiovascular risk in women with a history of preeclampsia points toward similarities between hypertensive disorders of pregnancy and other cardiovascular diseases. The study by Gennari-Moser et al is an important step in our understanding of the links between vasculogenesis and steroid synthesis, but many more such steps will have to follow.

**Disclosures**

None.

**Sources of Funding**

Dr Delles is supported by the European Commission collaborative project “EU-MASCARA” and a Chief Scientist Officer project grant ETM/196. Dr Freel is supported by a Clinician Scientist Fellowship from the Medical Research Council UK (G0802803).
References

Aldosterone, Vascular Endothelial Growth Factor, and Preeclampsia: A Mystery Solved?
Christian Delles and Ellen Marie Freel

Hypertension. 2013;61:958-960; originally published online March 4, 2013;
doi: 10.1161/HYPERTENSIONAHA.111.00767

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/61/5/958

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/