20-Hydroxyeicosatetraenoic Acid and Angiotensin
A Positive Feedback System to Cause Hypertension

John D. Imig

Arachidonic acid metabolites generated by cytochrome P450 (CYP) enzymes are now recognized as contributing importantly to vascular function and blood pressure regulation. CYP4A enzymes act as hydroxylases converting arachidonic acid to hydroxyeicosatetraenoic acids (HETEs), with 20-HETE being the major product. 20-HETE has both prohypertensive and antihypertensive actions depending on the specific CYP4A isoform expressed and its localization. 20-HETE generated by CYP4A and CYP4F enzymes in renal tubular cells will decrease sodium reabsorption to cause natriuresis and lower blood pressure. On the other hand, 20-HETE–Renin-Angiotensin System Interactions

angiogenesis and 20-HETE levels decreased in human renovascular hypertension. As further evidence that angiotensin increases 20-HETE, data in human hypertensive patients demonstrate increased plasma 20-HETE levels that correlate with plasma renin activity. These studies support the notion that vascular 20-HETE levels increase in response to angiotensin II; however, the potential influence of 20-HETE on the renin-angiotensin system had not been investigated previously. Gene microarray analysis of cultured endothelial cells that had been incubated with 20-HETE provided the unexpected data that 20-HETE increased ACE expression by 5.76-fold. Intriguingly, ACE gene expression demonstrated a far bigger increase in human microvascular endothelial cells than expression of numerous other genes. These findings suggested that positive feedback interactions between the vascular CYP4A2/20-HETE system and the renin-angiotensin system existed.

Experimental studies by Sodhi et al7 in this issue of Hypertension were conducted to evaluate the consequences of increased endothelial cell CYP4A2 expression on the renin-angiotensin system and blood pressure. As had been demonstrated previously, increased CYP4A2 expression in rats using a lentivirus expressing the CYP4A2 cDNA under the control of the endothelial-specific promoter (VECAD-CYP4A2) resulted in hypertension that could be reversed by 20-HETE or hydroxylase inhibition.5,7 Aortic ACE and angiotensin type 1 receptor mRNA and protein levels were increased in rats that had increased endothelial CYP4A2 expression. Plasma and aortic but not kidney angiotensin II levels were elevated in VECAD-CYP4A2 rats providing support to the idea that the hypertension was a consequence of vascular and not renal tubular angiotensin II actions. Alterations in renal hemodynamics likely contributed to the hypertension, because creatinine clearance was decreased in VECAD-CYP4A2 rats. As evidence for angiotensin dependence, hypertension in the VECAD-CYP4A2 rats was prevented or reversed by ACE or angiotensin type 1 receptor inhibition.

The findings of this study present a novel positive feedback system whereby 20-HETE and angiotensin II could result in severe vascular dysfunction in hypertension. Although potentially exciting, there is a complexity to the interactions between these systems in the kidney that makes it difficult to therapeutically target 20-HETE. One recent study demonstrated that combining hydroxylase inhibition with soluble epoxide hydrolase inhibition decreased blood pressure and improved kidney function in Ren-2 renin transgenic rats that have angiotensin-dependent hypertension.11 On the contrary, fenofibrate treatment to increase renal tubular 20-HETE generation prevented the development of angiotensin-dependent hypertension in mice.12 Interestingly, urinary 20-HETE levels decreased in human renovascular hypertension suggesting that renal tubular CYP4A enzymes respond to angiotensin II in an opposing direction.10 Taken together these findings suggest that 20-HETE inhibition could be beneficial for vascular dysfunction, but the ability to be antihypertensive would be questionable.

Perspectives
The report by Sodhi et al7 demonstrates a novel vascular interaction between the CYP4A2/20-HETE system and the
renin-angiotensin system that could potentiate vascular dysfunction in hypertension (Figure). A key question that remains is the endothelial cell signaling mechanisms by which 20-HETE increases ACE expression. Another avenue to be explored is the manipulation of this interaction to improve vascular function in hypertension and other cardiovascular diseases. Regardless, the experimental findings by Sodhi et al.7 in this issue of Hypertension have presented a novel paradigm that changes how interactions between 20-HETE and angiotensin in cardiovascular diseases will be evaluated in the future.

**Sources of Funding**
Advancing a Healthier Wisconsin and National Institutes of Health grants HL-59699 and DK38226 supported this work.

**Disclosures**
None.

**References**


20-Hydroxyeicosatetraenoic Acid and Angiotensin: A Positive Feedback System to Cause Hypertension
John D. Imig

Hypertension. 2010;56:822-823; originally published online September 13, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.156174

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/56/5/822

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/