Cytochrome P-450 Under Pressure
More Evidence for a Link Between 20-Hydroxyeicosatetraenoic Acid and Hypertension

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Considerable evidence links the metabolism of arachidonic acid by cytochrome P-450 (CYP) enzymes with the regulation of vascular tone and homeostasis as well as renal function. The enzymes in question fall into 2 classes: the epoxygenases, which generate vasodilator epoxyeicosatrienoic acids (EETs), and the ω/ω-1 hydroxylases, which generate the constrictor 20-hydroxyeicosatetraenoic acid (20-HETE).

See p 63

EETs act as endothelium-derived hyperpolarizing factors, and alterations in their formation and tissue levels contribute to the development of some forms of hypertension. For example, in spontaneously hypertensive rats (SHR) and in rats with angiotensin II–induced hypertension, inhibitors of the soluble epoxide hydrolase, which increase EET levels, markedly attenuate blood pressure; additionally, salt-induced hypertension in salt-sensitive Dahl rats has been linked with a failure to increase EET production. Moreover, a polymorphism of the CYP 2J2 epoxygenase, which results in the attenuated binding of the transcription factor Sp1 and reduced promoter activity, has been associated with an enhanced risk of developing coronary artery disease in humans. However, there is also evidence suggesting that a CYP 2C epoxygenase expressed in endothelial cells is able to generate superoxide anions (O₂⁻) in addition to EETs and in patients with coronary artery disease the inhibition of CYP 2C–derived O₂⁻ formation can markedly improve acetylcholine-induced vasodilation in the forearm vasculature.

When one searches for links between CYP expression and cardiovascular disease, it is perhaps more logical to look for changes in the production of a CYP-derived vasoconstrictor, in particular 20-HETE, which is currently characterized as a prohypertensive metabolite of arachidonic acid and is the predominant renal eicosanoid. Indeed, urinary 20-HETE levels were recently reported to be elevated in hypertensive and normotensive subjects with attenuated flow-induced vasodilation of the brachial artery. In the latter study, 20-HETE remained an independent predictor of an attenuated endothelium-dependent vasodilatation after adjustment for age, body mass index, and blood pressure. In women but not in men, higher 20-HETE levels were also associated with hypertension. Several groups have reported an altered expression of CYP 4A and production of 20-HETE in genetic and experimental models of hypertension. In the most thoroughly studied model, the SHR, ω-hydroxylase activity and intrarenal levels of 20-HETE are at their highest during the development of hypertension. Inhibition of ω-hydroxylase activity in SHR reduces 20-HETE production and blood pressure, and in vivo administration of CYP 4A1 antisense oligonucleotides has also been reported to reduce blood pressure as well as vascular reactivity in the mesenteric bed. A link between 20-HETE production and hypertension has also been forged in other animal models, including deoxycorticosterone acetate salt–induced and angiotensin II–induced hypertension, as well as in Lyon hypertensive rats (for review, see Sarkis and Roman).

Although 20-HETE is a vasoconstrictor and is thought to act as a second messenger for contractile agonists such as endothelin, angiotensin II, norepinephrine, and phenylephrine (for review, see Roman), an increase in 20-HETE is not always synonymous with an increase in blood pressure. Indeed, depending on the specific site of its generation, 20-HETE has the potential to play a dual role in the regulation of blood pressure by virtue of its ability to induce contraction, as well as to inhibit sodium reabsorption. This means that increased 20-HETE levels can be linked to the development of hypertension as well as to blood pressure reduction and, conversely, that a decrease in 20-HETE levels, which would be assumed to reflect a decrease in vascular contraction, can be associated with enhanced sodium reabsorption and thus hypertension (Figure). This also implies that it is difficult to predict the consequences of a change in the activity of a given CYP enzyme.

In this issue of Circulation, Gainer et al report that a loss-of-function variant of the human renal 20-HETE synthase, CYP 4A11, is associated with essential hypertension in a white population from Tennessee. The polymorphism in question (T8590C) resulted in the substitution of phenylalanine 434 by serine. However, rather than increasing 20-HETE production and generating hypertension by increasing vascular tone, the mutated protein exhibits an attenuated ability to generate 20-HETE and 19-HETE from arachidonic acid as well as 11- and 12-hydroxydocosanoic acids from lauric acid. The finding that a polymorphism associated with hypertension is linked to a decrease in enzyme activity would tend...
to suggest (unfortunately, 20-HETE levels were not determined in the blood or urine of the subjects analyzed by Gainer et al) that the effects are mediated at the level of the kidney and that a decrease in 20-HETE production is associated with an increase in sodium reabsorption. However, the mapping of CYP isoforms in the human kidney is far from complete, and there are probably several isoforms of CYP 4A and 4F ω-hydroxylases differentially expressed at different sites. Determining which enzyme is expressed in which region will be important to understand the molecular interactions that can link CYP polymorphism with hypertension. In the Sprague-Dawley rat, for example, there are 4 independently regulated CYP 4A isoforms that are differentially expressed along the nephron. Each of these CYP enzymes displays critical differences in the ability to generate 20-HETE, and 2 of them (CYP 4A2 and CYP 4A3) actually generate the functionally antagonistic products 20-HETE and 11,12-EET. Thus, although a decrease in the generation of 20-HETE by CYP 4A enzymes localized in the thick ascending limb may result in an increase in blood pressure (as reported in the salt-sensitive Dahl rat), an increase in the generation of 20-HETE in the vicinity of preglomerular microvessels would also be expected to increase afferent arteriolar tone and result in hypertension.

To date, only 2 putative renal 20-HETE synthases have been reported in humans, CYP 4A11 and CYP 4A22. However, although CYP 4A11 is the predominant isoform expressed in human kidneys, is readily detectable by Western blotting, and metabolizes arachidonic acid and lauric acid, Gainer et al found that CYP 4A22, which can only be detected at the mRNA level, does not encode a functional protein. The human CYP 4A11 gene is, however, homologous (78% identity at the nucleotide level) with the murine Cyp 4a14 gene, and the deletion of the latter resulted in hypertension. The increase in blood pressure was more marked in male than in female animals (mean arterial pressure of ≈134 versus 115 mm Hg, respectively) and could be normalized by castration. Gainer et al found no link between the T8590C polymorphism, gender, and hypertension in humans, which was somewhat disappointing given the clear androgen-sensitive changes in blood pressure in the Cyp 4a14−/− mice. However, there appear to be major differences in the CYP 4A homologues in question because, unlike the human CYP 4A11, the murine Cyp4a14 enzyme is not a 20-HETE synthase. Moreover, the consequences of Cyp 4a14 deletion were actually associated with an increase in renal 20-HETE production that could be attributed to the increased expression of a second Cyp 4a enzyme (Cyp 4a12) in close proximity to afferent arterioles. Enhanced Cyp 4a12 expression and 20-HETE formation in male mice coincided with increased afferent arteriolar resistance and an altered autoregulatory capacity. It remains to be determined whether an association exists between the CYP 4A11 T8590C polymorphism and the expression/activity of a second 20-HETE synthase in human kidneys.

The link between hypertension and the T8590C polymorphism in a white population from Tennessee was also observed as a trend in the Framingham offspring cohort, although the association was notably weaker. There is currently no good explanation that can account for these differences, but they can probably be attributed to additional confounding factors such as dietary salt intake and salt sensitivity, the renin-angiotensin system, body weight, and diabetes/sensitivity to insulin, all of which may influence 20-HETE production. However, although the molecular mechanisms underlying the development of hypertension in individuals carrying the T8590C polymorphism of the CYP 4A11 gene remain to be determined, the study by Gainer et al strengthens the hypothesis that abnormalities in the 20-HETE pathway are involved in various forms of human hypertension.
References


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