Does 20-Hydroxyeicosatetraenoic Acid Contribute to Sex Differences in Cardiovascular Risk by Increasing Oxidative Stress?

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Previous studies have indicated that there are large sex differences in the incidence of hypertension, and the role of androgens in enhancing the risk of cardiovascular disease is well recognized.1,2 However, the mechanisms by which androgens increase blood pressure are poorly understood. Recent studies have demonstrated that androgen-sensitive forms of hypertension are associated with increased production of 20-hydroxyeicosatetraenoic acid (20-HETE) in the kidney and the vasculature.3 However, the role of 20-HETE in this form of hypertension has not been established, because this pathway has both prohypertensive and antihypertensive actions.4 At the level of the renal tubule, upregulation of the formation of 20-HETE inhibits sodium transport and opposes the development of hypertension, whereas in the vasculature, 20-HETE is a potent vasoconstrictor that promotes hypertension.

The study of Singh et al5 in the current issue explores the role of 20-HETE in the development of endothelial dysfunction and hypertension in rats chronically treated with dihydrotestosterone. The results indicate that the expression cytochrome P450 4A protein and the production of 20 HETE increase in renal arteries of rats treated with dihydrotestosterone. The increase in vascular 20-HETE production is because of upregulation of the expression of the cytochrome P450 4A8 isoform. The development of hypertension in these studies was associated with the development of endothelial dysfunction, as reflected by an impaired vasodilator response to acetylcholine, increased expression of the gp-91 and gp-47 phox subunits of reduced nicotinamide-adenine dinucleotide phosphate oxidase, and increased superoxide production by the vasculature. More importantly, this study is the first to establish a cause-and-effect relationship among elevated vascular production of 20-HETE, endothelial dysfunction, and hypertension. To do this, these authors demonstrated that chronic treatment of the rats with a selective inhibitor of the synthesis of 20-HETE prevents the increases in vascular production of superoxide, endothelial dysfunction, and hypertension in rats treated with dihydrotestosterone. These studies strongly implicate elevated vascular production of 20-HETE as an essential mediator of endothelial dysfunction and the elevated vascular tone in androgen-induced hypertension.

The results of the present study have a number of implications. Previous studies indicated that 20-HETE plays an important role in the regulation of renal tubular and vascular function,4 but the role of this system in mediating oxidative stress and endothelial function has only been recognized recently when Wang et al6 reported that upregulation of vascular cytochrome P450 4A2 expression using an adenoviral vector increased the production of 20-HETE and impaired endothelial function. Subsequent studies have explored several mechanisms by which 20-HETE alters the response to endothelium-dependent vasodilators.7,8 These pathways are summarized in the Figure. It now appears that the vascular production of 20-HETE is elevated in spontaneous hypertensive rats and in angiotensin II– and androgen-induced models of hypertension.3,5,9,10 This is probably secondary to upregulation of the expression of cytochrome P450 4A isoforms by androgens, angiotensin II, sympathetic tone (catecholamines), and endothelin.4 Increased production of 20-HETE in the vasculature is associated with endothelial dysfunction and increased vascular tone, which contributes to the development of the elevated blood pressure in these models of hypertension. At least 3 different pathways play a role in this response. The study by Singh et al5 indicates that 20-HETE increases the vascular expression of subunits of reduced nicotinamide-adenine dinucleotide phosphate oxidase that produce superoxide. Other studies indicate that 20-HETE affects the association of endothelial NO synthase with heat shock protein 90, leading to diminished formation of NO and increased formation of superoxide.6,7 Finally, Guo et al8 reported recently that 20-HETE directly increases the formation of superoxide by endothelial cells. All of these changes in the vasculature diminish the bioavailability of NO, leading to endothelial dysfunction and hypertension.

As with any groundbreaking study, this article raises a number of questions that will have to be addressed in future studies. It is well known that endothelial dysfunction is a common feature associated with the development of nearly all forms of hypertension and diabetes. Thus, it will be important to determine whether upregulation of the vascular production of 20-HETE is a common pathway in the development of endothelial dysfunction or if this is limited to androgen-induced hypertension. Another intriguing question is whether upregulation of vascular 20-HETE production contributes to the elevated risk of heart attack and stroke in male hypertensive patients. This question is of great clinical interest in light of recent findings that inhibitors of 20-HETE...
Role of cytochrome P450 (CYP450) 4A enzymes in contributing to superoxide production, impaired vascular relaxation, and reduced NO availability in hypertension. Angiotensin II, endothelin, androgens, and catecholamines increase the expression of CYP4A enzymes in the vasculature. Elevated vascular production of 20-HETE contributes to increased vascular resistance via direct vasoconstrictor effects and through uncoupling of NO synthetase (NOS) by promoting the dissociation of heat shock protein 90 from endothelial NO synthase (eNOS). This favors the production of superoxide (O$_2^-$) rather than NO by eNOS. CYP450 enzymes can also form O$_2^-$ directly. Increased O$_2^-$ scavenge NO and oxidize tetrahydrobiopterin (BH$_4$) to dihydrobiopterin (BH$_2$). This further promotes eNOS uncoupling and additional O$_2^-$ formation. Reduced NO levels then contribute to the endothelial dysfunction and the development of hypertension.

reduce cerebral vasospasm after subarachnoid hemorrhage and reduce infarct size after transient ischemia and reperfusion of the heart and the brain. Another question is the relative importance of changes in the renal versus vascular production of 20-HETE in androgen-induced and other forms of hypertension. For example, the present study indicates that 20-HETE production is increased in the vasculature and that this promotes vasoconstriction and the development of hypertension. However, one has to wonder whether infusion of dihydrotestosterone also induces the production of 20-HETE in the kidney, which would promote natriuresis. It will be important to determine in the future whether this reflects differential regulation of the cytochrome P450 4A isoforms in kidney versus the vasculature and to what extent this can help explain why inhibitors of 20-HETE formation lower blood pressure in some models of hypertension (spontaneously hypertensive rats, angiotensin II–induced, and androgen-induced), but a deficiency in the renal formation of 20-HETE is associated with the development of salt-sensitive hypertension in normotensive Sprague–Dawley and in Dahl salt-sensitive rats.

Clearly, more work is needed to address these issues, but it now appears that elevated vascular production of 20-HETE contributes to endothelial dysfunction and the development of hypertension and cardiovascular disease in spontaneously hypertensive rats and in angiotensin II– and androgen-induced models of this disease. Sex differences in the expression of cytochrome P450 4A isoforms and the production of 20-HETE in the vasculature may also underlie some of the cardiovascular protection afforded premenopausal women.

Sources of Funding

This work was supported in part by National Institutes of Health grants HL36279 and HL29587.

Disclosures

None.

References

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Hypertension. 2007;50:37-38; originally published online June 4, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.090803

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