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20-HETE and Blood Pressure Regulation:

Clinical Implications

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Abstract

20-Hydroxy-5, 8, 11, 14-eicosatetraenoic acid (20-HETE) is a cytochrome P450 (CYP)–derived omega-hydroxylation metabolite of arachidonic acid. 20-HETE has been shown to play a complex role in blood pressure regulation. In the kidney tubules, 20-HETE inhibits sodium reabsorption and promotes natriuresis, thus, contributing to antihypertensive mechanisms. In contrast, in the microvasculature, 20-HETE has been shown to play a pressor role by sensitizing smooth muscle cells to constrictor stimuli and increasing myogenic tone, and by acting on the endothelium to further promote endothelial dysfunction and endothelial activation. In addition, 20-HETE induces endothelial angiotensin-converting enzyme, thus, setting forth a potential feed forward prohypertensive mechanism by stimulating the renin–angiotensin–aldosterone system. With the advancement of gene sequencing technology, numerous polymorphisms in the regulatory coding and noncoding regions of 20-HETE–producing enzymes, CYP4A11 and CYP4F2, have been associated with hypertension. This in-depth review article discusses the biosynthesis and function of 20-HETE in the cardiovascular system, the pharmacological agents that affect 20-HETE action, and polymorphisms of CYP enzymes that produce 20-HETE and are associated with systemic hypertension in humans.

Keywords

20-HETE; hypertension; CYP4F2; CYP4A11; androgen; angiotensin-converting enzyme

20-Hydroxy-5, 8, 11, 14-eicosatetraenoic acid (20-HETE) is the omega (ω)-hydroxylation metabolite of arachidonic acid formed by cytochrome P450 (CYP) monooxygenases of the CYP4 gene family. 20-HETE has been shown to play a complex role in blood pressure regulation, having effects on vascular tone and water and salt balance. The report by Sacerdoti et al¹ showing that depletion of CYP450 normalizes blood pressure in the

spontaneously hypertensive rat (SHR) was the first to implicate 20-HETE in the pathogenesis of hypertension. Consequently, numerous studies in animal models and humans have provided ample evidence that either a deficiency in tubular 20-HETE biosynthesis or increased vascular 20-HETE contributes to hypertension.² Moreover, single nucleotide polymorphisms (SNPs) in CYP4A11 and CYP4F2, enzymes that produce 20-HETE, have been linked to a risk of developing hypertension. This in-depth review article discusses the biosynthesis and function of 20-HETE in the cardiovascular system, the pharmacological agents that affect 20-HETE action, and polymorphisms of CYP enzymes that produce 20-HETE and associate with hypertension in humans.

20-HETE BIOSYNTHESIS, METABOLISM, AND RELEASE

20-HETE is a bioactive eicosanoid derived from the ω -hydroxylation of arachidonic acid by enzymes of the CYP4 gene family. The CYP4 gene family comprises 30 proteins that are divided into 3 subfamilies (CYP4A, CYP4B, and CYP4F), all of which catalyze the hydroxylation of the terminal carbon and the (ω -1) carbon of saturated and unsaturated fatty acids. CYP4 proteins share high sequence similarity and common catalytic properties; however, their expression pattern in the tissue and their hormonal regulation differ. Arachidonic acid metabolism by CYP4A and CYP4F occurs in multiple organs: liver, kidney, heart, lung, brain, and the vasculature.^{3–12} Both the CYP4A and CYP4F subfamilies produce 20-HETE in animals and humans to varying degrees.^{13,14} The major 20-HETE-producing CYP4 isoforms are CYP4F2 and CYP4A11 in humans^{15,16}; CYP4A1, CYP4A2/3, CYP4A8, CYP4F1, and CYP4F4 in rats^{17,18}; and *cyp4a12* in mice.^{19,20} The expression pattern of CYP4F is species-specific; it is found in the mouse glomerulus, rat kidney, rabbit aortic vascular smooth muscle cells, and human kidney and liver.^{17,21–24} Furthermore, different species have different isoforms: 4 CYP4F isoforms in the rat (4F1, 4F4, 4F5, and 4F6) and 2 in humans (4F2 and 4F3), which can produce 20-HETE.²⁴ In the mouse, the catalytic activity of the 5 *Cyp4f* isoforms (4f13, 4f14, 4f15, 4f16, and 4f18) for producing 20-HETE is unknown.²¹ CYP4F2 is the major 20-HETE-producing enzyme in the human kidney. Studies by Lasker et al¹⁵ suggest that up to 70% of the 20-HETE found in human kidney microsomes comes from CYP4F2-catalyzed metabolism of arachidonic acid.

The CYP4A isoforms are also found in multiple species, including humans, rats, mice, and rabbits. Different species have different isoforms of the CYP4A enzyme. In the mouse, the 3 *Cyp4a* isoforms (*Cyp4a10*, *Cyp4a12*, and *Cyp4a14*) have the ability to convert arachidonic acid to 20-HETE. However, among those proteins, only *Cyp4a12* shows a significant 20-HETE synthase activity.¹⁹ There are 2 *Cyp4a12* genes that express *Cyp4a12*: *Cyp4a12a* and *Cyp4a12b*. Both genes are the product of a tandem 100-kb duplication within the *Cyp4abx* cluster.²⁵ The expression pattern of *Cyp4a10*, *Cyp4a12*, and *Cyp4a14* exhibits sex differences. *Cyp4a10* is expressed in both males and females, *Cyp4a12a* is male-specific and androgen-regulated, and *Cyp4a14* is highly expressed in females.^{19,20,26} As indicated above, *Cyp4a12a* is the predominant 20-HETE synthase.^{19,27} With respect to the rat counterparts, *Cyp4a10*, *4a12*, and *4a14* are murine homologues of rat CYP4A1, 4A8, and 4A2/4A3.²⁸ In the rat kidney, CYP4A1, CYP4A3, and CYP4A8 are highly expressed in the S1, S2, S3 segments of the proximal tubules; CYP4A2 is expressed in the outer-medullary thick

ascending limb and renal vasculature.^{3,29} Different isoforms have distinct catalytic activities.^{18,24,30} Rat CYP4A1 and CYP4A8 specifically catalyze ω/ω -1-hydroxylation of arachidonic acid, whereas CYP4A2 and CYP4A3, in addition to ω/ω -1-hydroxylation, catalyze 11,12-epoxidation of arachidonic acid.^{18,31} Furthermore, CYP4A proteins are believed to be the predominant arachidonic acid ω/ω -hydroxylases in both rats and mice, although CYP4F proteins are also present.³²

In humans, the predominant CYP4A isoforms are CYP4A11 and CYP4A22. CYP4A11 is mostly present in the S2 and S3 segments of the proximal tubules.^{15,33} The localization of 20-HETE synthesis along the nephron parallels the expression of the CYP4 proteins. CYP4A22 mRNA has also been detected in the human kidney; however, work by Gainer et al¹⁶ suggests that it is a nonfunctional protein. In the rat vasculature, CYP4A proteins show a distinct distribution along the vascular tree where their expression increases with decreased vascular diameter.²⁹ Likewise, the rate of 20-HETE biosynthesis is inversely proportional to blood vessel diameter.²⁹ 20-HETE is not detected in large conduit vessels,²⁹ therefore, it is largely believed that 20-HETE is an eicosanoid of the microcirculation.

The synthesis and release of 20-HETE is regulated by numerous autacoids including angiotensin II (Ang II), endothelin-1, serotonin [5-hydroxytryptamine (5-HT)], and other growth factors.^{10,34} Clinically, patients with renovascular disease have an increase in the expression of the renin-angiotensin system and elevated levels of Ang II, which parallels an increase in plasma 20-HETE.³⁵ Inhibition of 20-HETE synthesis attenuates Ang II-mediated hypertension by 40% in rats.³⁶ Endothelin-1, the most potent vasoconstrictor, also promotes the release of 20-HETE from the rat kidney, whereas inhibition of CYP-dependent 20-HETE production attenuates the renal vascular response to endothelin-1.³⁷ 20-HETE has been shown to negatively regulate endothelin-1, and the ability of endothelin-1 to stimulate the secretion of atrial natriuretic peptide from the heart is blocked by an inhibitor of 20-HETE synthesis.³⁸ Cerebral vessels during subarachnoid hemorrhage have increased 20-HETE synthesis through 5-HT-mediated activation of the 5-HT_{1B} receptor. This increase in vascular 20-HETE contributes to the vasoconstrictor response to 5-HT.³⁹ In addition, both parathyroid hormone and epidermal growth factor have been shown to stimulate 20-HETE production in the kidneys of SHR.^{5,40} More recently, multiple studies have shown that androgen increases CYP4A expression and 20-HETE production in renal interlobar arteries.^{32,41,42} 20-HETE synthesis in the renal and cerebral arteries is inhibited by nitric oxide (NO), carbon monoxide, and superoxide radicals.^{12,43-49}

Exogenous factors can also affect the production and release of 20-HETE. Lipid-lowering agents such as fibrates induce CYP4A1 and CYP4A3 expression in the liver and kidney.⁵⁰ Treatment of Dahl salt-sensitive (SS) hypertensive rats with clofibrate increases levels of 20-HETE and prevents the development of SS hypertension.⁵⁰ Similar effects are observed upon treatment with fenofibrate, another hypolipidemic drug.⁵¹ Interestingly, CYP4A expression in the blood vessels that do not express peroxisome proliferator-activated receptor- α (PPAR α) is not induced by fibrates.^{52,53} Dietary consumption also alters the synthesis of 20-HETE. A high-fat diet reduces CYP4A activity and decreases the production of 20-HETE in male rats. Induction of 20-HETE by clofibrate also attenuates high-fat diet-induced hypertension in rats.⁵⁴ Diets high in sodium increase the expression of multiple

CYP4A isoforms, including CYP4A2, CYP4A3, and CYP4A8 in mesenteric arteries from normotensive rat, whereas diets low in sodium upregulate CYP4A3.⁵⁵ Further clinical studies also suggest that plant lignans can modulate levels of 20-HETE. Patients receiving sesame supplementation in the form of sesamin have lower plasma 20-HETE and urinary 20-HETE levels. Furthermore, sesamin inhibits the activity of CYP4A11 and CYP4F2 in renal and liver microsomes.⁵⁶ Age and sex have also been shown to affect 20-HETE levels.⁴² The age-dependent increase in 20-HETE synthesis has been shown in cortical microsomes from SHR, normotensive rats, and Dahl rats.^{5,57}

Metabolism of 20-HETE occurs through many of the similar pathways that metabolize arachidonic acid, including cyclooxygenases (COX), lipoxygenases, and CYP monooxygenases. 20-HETE can also be metabolized by alcohol dehydrogenases and β -oxidation.⁵⁸ 20-Hydroxy-prostaglandins are COX-derived metabolites of 20-HETE that have been shown to add to the 20-HETE-mediated constrictor response of rat aortic rings. Inhibition of COX decreased 20-HETE-mediated constriction in a dose-dependent manner.⁵⁹ This phenomenon is not seen in all vascular beds. 20-HETE-induced vasoconstriction in rat afferent arterioles is COX-independent.³ 20-HETE is also metabolized by alcohol dehydrogenases to 20-carboxy-arachidonic acid. Studies have shown that 20-carboxy-arachidonic acid is a potent vasodilator in porcine coronary microvessels.⁵⁸ It also acts as an activator of PPAR α/γ in COS-7 cells.⁶⁰ 20-HETE undergoes β -oxidation to 18-, 16-, and 14 β -oxidation products.⁵⁸ In platelets and polymorphonuclear leukocytes, 20-HETE can be metabolized by lipoxygenases and COX to inactive products.^{61,62} CYP epoxygenases, such as CYP2C23, metabolize 20-HETE to 20-hydroxy-epoxyeicosatrienoic acid (EETs) in rat kidney, which have been shown to act as PPAR α activators⁶³ and contribute to the anti-inflammatory and protective properties of lipid-lowering drugs.⁶⁴ In the liver and kidney, 20-HETE is esterified into phospholipids and stored.³⁴

The aforementioned studies clearly indicate that (1) 20-HETE biosynthesis occurs in many cell types and tissues; (2) it is formed by CYP4A and 4F enzymes; (3) its synthesis is regulated by hormones, vasoactive autacoids and by diet and age; (4) once formed, it is subjected to metabolism by other eicosanoid-producing enzymes and to esterification, glucuronate conjugation, and ω -oxidation; and (5) its levels are readily detected in biological fluids, including blood and urine.

PHARMACOLOGIC AGENTS AFFECTING 20-HETE BIOSYNTHESIS AND ACTION

Over the years, many pharmacological inhibitors, both nonselective and selective, have been developed to inhibit 20-HETE synthesis.^{24,65} One-aminobenzotriazole is a CYP inhibitor that requires the catalytic formation of benzyne with selectivity toward the CYP4 family.⁶⁶ 17-Octadecynoic acid is a suicide inhibitor of CYP, which inhibits the formation of both 20-HETE and epoxyeicosatrienoic acids.⁶⁷ N-methylsulfonyl-12,12-dibromododec-11-enamide and 12-dibromodibenzo-p-dioxin (DBDD) are other structure-based inhibitors of CYP that are effective in inhibiting 20-HETE synthesis.⁶⁸ N-(3-Chloro-4-morpholin-4-yl)Phenyl-N'-hydroxyimido formamide (TS011) has been shown to inhibit 20-HETE synthesis in a dual hemorrhage model of subarachnoid hemorrhage in dogs.⁶⁹ One of the more recently

identified inhibitors is N-hydroxy-N'-(4-butyl-2-methylphenyl) formamidine (HET0016), which is the most potent inhibitor of 20-HETE synthesis in vivo and is highly specific for blocking the CYP4-catalyzed ω -hydroxylation.^{70,71} Recent studies in our laboratory have shown that hydralazine can inhibit 20-HETE synthesis in renal microsomes from normotensive rats without affecting the synthesis of other CYP-derived arachidonic acid metabolites, such as epoxyeicosatrienoic acids (unpublished data).

Falck and others^{36,72} designed and synthesized, in addition to inhibitors, numerous 20-HETE analogues, which are now commonly used to mimic or inhibit 20-HETE-mediated signaling. 20-Hydroxyeicosa-6(Z), 15(Z)-dienoic acid (20-6,15-HEDE) and 20-hydroxyeicosa-6(Z), 15(Z)-dienoylglycine (20-6,15-HEDGE) are both stable analogues of 20-HETE that can block the vasoconstrictor actions of 20-HETE.^{36,72} In contrast, 20-hydroxyeicosa-5(Z), 14(Z)-dienoic acid (5, 14-20-HEDE) and N-20-hydroxyeicosa-5(Z), 14(Z)-dienoyl]glycine (5,14-20 HEDGE) are 20-HETE mimetics.⁷²⁻⁷⁴ These compounds serve as excellent tools to discern the role of 20-HETE in health and disease. Major efforts are currently being undertaken to improve the bioavailability of these compounds and to design additional compounds that will aid in identifying the cellular target(s) of 20-HETE to further explore whether a cellular receptor for 20-HETE exists.

TUBULAR EFFECTS OF 20-HETE

In the kidney nephron, the synthesis of 20-HETE has been localized to the proximal tubule (S1, S2, S3),^{5,75} medullary thick ascending limb of Henle (TALH),⁷⁶ and glomerulus.⁴ 20-HETE mediates sodium and water transport through the regulation of various channels and cotransporters dependent on the localization within tubules. In the proximal tubules, 20-HETE inhibits Na⁺-K⁺-ATPase activity via protein kinase C (PKC)-dependent phosphorylation of the Na⁺-K⁺-ATPase α subunit at serine 23 residue⁷⁷ and mediates the inhibitory effects of parathyroid hormone,⁷⁸⁻⁸¹ dopamine,⁷⁷ endo-thelin,⁸² and Ang II^{34,83} on Na⁺-K⁺-ATPase activity in the proximal tubule. In the medullary TALH, 20-HETE prevents K⁺ efflux and Na⁺ reabsorption by inhibiting the large conductance 70 pS K⁺ channel and the Na⁺-K⁺-2Cl⁻ cotransporter,^{84,85} and decreasing transepithelial potential and chloride transport.⁴ Administration of inhibitors of 20-HETE blocks tubuloglomerular feedback.^{86,87} The inhibitory effects of Ang II,^{76,88} bradykinin,⁸⁹ and elevation in intracellular Ca²⁺,⁹⁰⁻⁹² on Na⁺ transport in the TALH are also dependent on the formation of 20-HETE.

The kidney plays an important role in the regulation of arterial pressure via the pressure-natriuretic response,⁹³ which is associated with elevations in renal medullary blood flow,⁹⁴⁻⁹⁶ renal interstitial hydrostatic pressure,⁹⁷⁻¹⁰¹ and inhibition of Na⁺ transport in the proximal tubule.¹⁰²⁻¹⁰⁴ 20-HETE has been shown to play an important role in the regulation of the pressure-natriuretic response. An increase in renal perfusion pressure contributes to increased 20-HETE levels in renal cortex. Inhibitors of 20-HETE synthesis maintain Na⁺-K⁺-ATPase activity and prevent the internalization of sodium-hydrogen exchanger 3 protein in the proximal tubule and impair the pressure-natriuretic response of rats by 50%.^{98,105} The benefit of 20-HETE synthesis in the tubules has been suggested and demonstrated in various studies. Inhibition of 20-HETE synthesis in the medullary TALH¹⁰⁶ and outer medullary

regions¹⁰⁷ has been shown to increase blood pressure and sodium reabsorption in Lewis rats. Stimulation of the renal formation of 20-HETE with clofibrate, a PPAR agonist that upregulates CYP4A proteins, lowers blood pressure in Dahl SS,⁵⁰ deoxycorticosterone acetate-salt¹⁰⁸ and high-fat-induced hypertensive rats.⁵³ The importance of reduction in outer medullary renal 20-HETE to SS hypertension was further demonstrated by Stec et al,¹⁰⁹ who crossed the Dahl SS rats, which exhibit decreased CYP4A2 protein levels in the outer medulla, with the Lewis strain rats. The resulting F₂ progeny demonstrated that the CYP4A2 allele cosegregates with the development of salt-induced hypertension.¹⁰⁹ Williams et al¹¹⁰ also showed that the transfer of chromosome 5 containing the CYP4A genes from Brown Norway rats on the Dahl SS genetic background increases the renal expression of CYP4A protein and the production of 20-HETE and that 20-HETE contributes to the antihypertensive and renoprotective effects seen in the SS.5 (Brown Norway) consomic strain. Also, in humans a deficiency in tubular 20-HETE synthesis and/or action measured as decreased urinary excretion in response to salt loading has been linked to SS hypertension.¹¹¹ Polymorphisms in the CYP4A11 gene that reduce its catalytic activity by more than 50% are associated with a decrease in the urinary excretion of 20-HETE and the development of SS hypertension in humans.^{112,113}

The glomerulus is another site of 20-HETE synthesis and action.⁴ Transforming growth factor-beta (TGF- β) production is upregulated in the glomeruli in Dahl SS rats¹¹⁴ and is associated with the elevation of glomerular capillary pressure¹¹⁵ and permeability of the glomerulus to albumin (Palb).¹¹⁶ TGF- β is found to directly increase Palb in isolated glomeruli and inhibits the formation of 20-HETE. Administration of 20-HETE prevents the effects of TGF- β on Palb.¹¹⁶ Thus, in the glomeruli 20-HETE is critical in maintaining a glomerular filtration barrier to albumin, and inhibition of 20-HETE synthesis may contribute to TGF- β -mediated glomerular injury in hypertension. In all, the abovementioned studies provide strong evidence that tubular synthesis and actions of 20-HETE are renal protective and antihypertensive.

VASCULAR EFFECTS OF 20-HETE

As indicated above, 20-HETE has been recognized as an eicosanoid of the microcirculation with renal, cerebral, cardiac, and mesenteric arteries having been shown to be rich sources of 20-HETE.^{24,29,117} Within the vascular wall, 20-HETE biosynthesis is primarily localized to the smooth muscle cells.³² The ability of the vascular endothelium to produce 20-HETE has only been demonstrated in the pulmonary circulation.¹¹⁸ 20-HETE's effects on vascular function are multifaceted and include stimulation of smooth muscle contractility, migration, and proliferation, and activation of endothelial cell dysfunction, angiogenesis, and inflammation (listed below). Such effects could have significant implications with regard to the development of hypertension and its cardiovascular complications.

20-HETE and Smooth Muscle Contractility

20-HETE participates in the regulation of vascular tone by sensitizing vascular smooth muscle cells to constrictor stimuli such as Ang II, phenylephrine, and endothelin,¹¹⁹ and by contributing to the myogenic response.^{11,24,120–122} Its synthesis and/or release is induced by Ang II,^{10,123,124} endothelin,^{124,125} and serotonin³⁹ and is also increased after treatment with

nitric oxide synthase (NOS) inhibitors.⁴⁶ In 1989, Escalante et al¹²⁶ first documented the vasoconstrictive effects of 20-HETE, which in the rat aorta was determined to be COX-dependent. Interestingly, these findings were different in the microcirculation as studies showed that the constrictor activity of 20-HETE is largely COX-independent.^{11,127} 20-HETE can also activate PKC, mitogen-activated protein kinase (MAPK), and src-type tyrosine kinase. All of the aforementioned kinases can phosphorylate and inhibit the conductance Ca^{2+} -activated K^{+} channels, leading to depolarization and elevation in cytosolic $[\text{Ca}]^{2+}$. This leads to an increase in opening and Ca^{2+} entry through the L-type Ca^{2+} channels.²⁴ 20-HETE alone also increases the conductance of L-type Ca^{2+} channels through activation of PKC. Recent work by Inoue et al¹²⁸ showed that 20-HETE enhances the conductance of inward nonselective cations and amplifies myogenic tone through synergistic activation of vascular transient receptor potential canonical 6. 20-HETE can also act through Rho kinase to maintain the phosphorylated status of myosin light chain 20 and increase the contractile apparatus to Ca^{2+} .¹²⁹ Modulation of CYP4A protein levels in small arteries and arterioles affects vascular reactivity and myogenic tone: overexpression of CYP4A leads to increased vascular reactivity and myogenic tone, whereas downregulation attenuates vascular reactivity and myogenic tone.^{130–132} These effects may contribute to a 20-HETE-mediated increase in blood pressure and the development of hypertension in experimental models.^{32,41,133–135} Other notable effects of 20-HETE on smooth muscle function are its ability to increase migration and stimulate proliferation; 2 actions that may contribute to remodeling in hypertension.^{136,137}

20-HETE and Endothelial Dysfunction

Although the capacity of the vascular endothelium to produce 20-HETE is questionable in most circulatory districts, its ability to respond to 20-HETE has been extensively studied. The vascular endothelium is important in the regulation of vascular tone, vessel diameter, and blood flow. It is also the first layer of defense against noxious stimuli.¹³⁸ The integrity of the endothelium is dependent on many factors, including NO, which is generated from L-arginine by endothelial nitric oxide synthase (eNOS).¹³⁹ *Endothelial dysfunction* is a term that describes the loss of NO bioavailability due to the diminished production or increased metabolism/degradation of NO and/ or an imbalance in the relative contribution of endothelium-derived relaxing and contracting factors. Several studies have shown that endothelial dysfunction is a feature of hypertension and an early risk factor for cardiovascular disease.^{140,141} Frisbee et al¹⁴² first suggested that 20-HETE plays a role in NO homeostasis. In their study, they showed that 20-HETE attenuated the effect of acetylcholine-induced relaxation in cremasteric arterioles. Studies from our laboratory provided ample evidence to support a causative relationship between the CYP4A–20-HETE pathway and endothelial dysfunction, both in vitro and in vivo. Rats transduced with adenovirus expressing the rat CYP4A2 cDNA demonstrated increased expression of CYP4A2 protein and production of 20-HETE in renal arteries and were hypertensive. Renal interlobar arteries from rats transduced with the CYP4A2 cDNA displayed endothelial dysfunction of renal interlobar arteries, which displayed reduced vasodilator responses to acetylcholine, reduced levels of NO and cyclic guanosine monophosphate, and increased levels of superoxide anion.¹⁴³ Targeted vascular endothelial overexpression of CYP4A2 in normotensive rats also leads to hypertension and endothelial dysfunction.^{135,144} Similar

results were seen in the androgen-induced hypertension rat model in which the vascular expression of CYP4A8 and production of 20-HETE were upregulated and were accompanied by a decrease in acetylcholine-mediated vasodilation.^{32,145} In all models, inhibition of 20-HETE synthesis abrogated the respective vascular dysfunction and hypertension. Further analysis revealed that 20-HETE interferes with the NO-dependent component of acetylcholine-induced relaxation without affecting the NO-independent component of the relaxing response to acetylcholine. This suggests that 20-HETE interferes with NO synthesis and/or bioavailability.¹⁴³ The link between 20-HETE levels and endothelial dysfunction is also seen in hypertensive individuals.¹¹³ It should be noted that in the pulmonary circulation, 20-HETE is produced by the vascular endothelium and has been shown to increase relaxation by activating eNOS.^{146,147}

A thorough examination of the relationship between 20-HETE and the eNOS-NO pathway was assessed using in vitro models. In cultured endothelial cells, 20-HETE uncouples eNOS by inhibiting the association of HSP90 with eNOS, reducing NO production and bioavailability.¹⁴⁸ Additional studies indicated that 20-HETE-mediated eNOS uncoupling and endothelial dysfunction are endothelial growth factor receptor, MAPK-, and I κ B kinase (IKK)-dependent.¹⁴⁹ The interaction between 20-HETE and eNOS was also studied in endothelial cells of other vascular beds. Ward et al¹⁵⁰ further showed that in human umbilical vein endothelial cells, chronic activation of activated protein kinase inhibited 20-HETE-mediated dissociation of eNOS from HSP90. Studies using several animal models^{32,135,143,151} have implicated 20-HETE as an important determinant of endothelial dysfunction in the microcirculation, adding to the mechanisms underlying the prohypertensive effect of 20-HETE.

20-HETE, Endothelial Activation, and Vascular Inflammation

Vascular wall inflammation contributes to the pathogenesis of various diseases, including atherosclerosis, cardiovascular disease, and hypertension. Recent studies suggest that inflammation-mediated vascular remodeling contributes to increased vascular resistance. Indeed, increases in wall thickness and wall/lumen ratio of resistance arteries have been associated with increases in blood pressure,^{152,153} implicating inflammation in the pathophysiology of hypertension.¹⁵⁴ Proinflammatory changes in endothelial phenotype, termed as endothelial activation, lead to an increase in cellular adhesion molecules, endothelial-leukocyte interaction, and permeability.^{155–157} The release of cytokines and chemokines, including monocyte chemoattractant protein-1, by activated endothelial cells further contribute to the migration/adhesion of monocytes through the chemokine receptor type 2.^{158,159} 20-HETE has been shown to induce proinflammatory changes in endothelial cells, including stimulation of adhesion molecule expression and cytokine release.¹⁶⁰ Downregulation of these inflammatory molecules abrogates inflammation and the associated vascular dysfunction and activation in an Ang II-induced hypertensive model.^{161,162}

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is a proinflammatory transcriptional activator.^{163,164} There is increasing support showing that NF- κ B activation and reactive oxygen species (ROS) play a key role in endothelial activation and subsequent inflammation in cardiovascular diseases.^{157,163,165–170} NF- κ B

activation induces the transcription of a large number of genes related to vascular inflammation. Inhibition of NF- κ B attenuates endothelial activation and ameliorates atherosclerosis, reduces Ang II-induced hypertension, and prevents Ang II-induced end-organ damage.^{154,171,172} NF- κ B is activated by numerous mediators, many of which act through ROS-dependent pathways.^{157,163} An increase in the level of vascular 20-HETE is associated with increased expression of the NADPH oxidase system and increased vascular superoxide anion production.^{32,143} Further studies in vitro showed that treatment of endothelial cells with 20-HETE led to increased ROS and NF- κ B activity. This resulted in endothelial activation characterized by increased expression of intracellular adhesion molecule and interleukin-8 levels.¹⁶⁰ Incubation of human endothelial cells with inhibitors of NF- κ B activation or MAPK prevented the 20-HETE-mediated increase in levels of adhesion molecules (ie, intracellular adhesion molecule-1).¹⁶⁰ This suggests that 20-HETE plays a role in endothelial activation and inflammation, thus contributing to hypertension. Importantly, in the rat model of androgen-induced and 20-HETE-dependent hypertension, administration of parthenolide (an IKK inhibitor) prevented endothelial dysfunction and lowered blood pressure, suggesting that IKK activation is a key signaling step for 20-HETE-induced endothelial dysfunction.¹⁴⁵

20-HETE and Oxidative Stress

20-HETE has been shown to increase oxidative stress by stimulating the production of superoxide and other ROS.¹⁷³ Renal inter-lobar arteries from androgen-treated rats that overexpress CYP4A and produce increased amounts of 20-HETE have two- to threefold increases in protein expression of NADPH oxidase subunits, p47phox and gp91phox. This is accompanied by an increase in vascular superoxide levels.³² Similar findings were seen in arteries from rats transduced with the CYP4A2 adenovirus.^{135,143} These results are of clinical significance as hypertensive patients have been shown to exhibit oxidative stress (measured via F2-isoprostane levels), which was closely correlated with an increase in urinary 20-HETE excretion.¹⁷⁴ Studies using endothelial cells demonstrated that 20-HETE stimulates superoxide production by mechanisms that include eNOS uncoupling and activation of NADPH oxidase-dependent and -independent pathways.^{148,175,176}

20-HETE AND THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system (RAS) is a key regulator of blood pressure and body fluid homeostasis. Components of the RAS include renin, angiotensin-converting enzyme (ACE), and angiotensin type 1 receptor (AT1R), which are generally expressed throughout the body in tissues that impact blood pressure modulation. Ang II, the product of sequential degradation of angiotensinogen by renin and ACE, and the final effector of the RAS system, increases blood pressure by: (1) vasoconstriction via AT1R activation, increased sympathetic tone and the release of arginine vasopressin; and (2) modulation of renal sodium and water reabsorption by stimulating renal AT1R, the production and release of aldosterone or the sensation of thirst in the central nervous system. AT1R blockers or ACE inhibitors are vastly used for the treatment of hypertension. In animal models, mice null for angiotensinogen, renin, ACE, and AT1RA (the closest murine homologue to the single human AT1R gene) exhibit a marked reduction in blood pressure, indicating the role of RAS

in normal blood pressure homeostasis.^{177,178} The interactions between 20-HETE and the RAS occur at several levels. On the one hand, Ang II has been shown to stimulate the release of 20-HETE in isolated preglomerular vessels¹⁰ and the renal synthesis of 20-HETE.¹⁷⁹ The stimulatory effect of Ang II on 20-HETE synthesis in preglomerular arteries was Ang II type 2 (AT2) receptor-dependent. AT2-dependent increase in 20-HETE was also observed in human platelets and neutrophils treated with Ang II.¹⁸⁰ 20-HETE has been shown to mediate responses to Ang II. Hence, increased production of 20-HETE in the peripheral vasculature contributes to the acute vasoconstrictor response to Ang II,¹⁸¹ whereas acute¹⁸² and chronic¹⁸³ inhibition of 20-HETE synthesis attenuates the renal pressor response to Ang II and the development of Ang II-dependent hypertension, respectively. In cultured aortic vascular smooth muscle cells, 20-HETE mediates Ang II-induced mitogenic effects. This may contribute to the vascular injury, hypertrophy, and hypertension caused by Ang II in rats.^{136,184,185} To this end, experimental models of hypertension that show increased vascular 20-HETE production, such as the SHR^{32,151} and androgen-induced hypertension in rats and mice,^{19,20,32,135} are also RAS-mediated.

On the other hand, recent studies from our laboratory have shown that 20-HETE activates the RAS via induction of vascular ACE. In endothelial cells, 20-HETE is a potent inducer of ACE expression. Treatment of human microvascular endothelial cells with exogenous 20-HETE induces ACE mRNA, increases ACE protein levels and ACE activity, all of which can be abolished in the presence of 20-HETE.¹⁸⁶ The mechanisms by which 20-HETE induces ACE include activation of endothelial growth factor receptor, phosphorylation of MAPK, and activation of the IKK complex with subsequent nuclear translocation of NF- κ B.¹⁸⁶ Increased expression and synthesis of 20-HETE, as in the CYP4A2-transduced rats¹⁴⁴ or the androgen-treated rats (data unpublished), is associated with increased expression of renal and vascular ACE, which is abolished by treatment with 20-HETE synthesis inhibitors. In the model of 20-HETE-dependent hypertension (rats overexpressing the CYP4A2 in the vascular endothelium), blood pressure is normalized by ACE inhibition or AT1R blockade.¹⁴⁴ This suggests the presence of a feed-forward amplification of 20-HETE-induced vascular dysfunction by the RAS. Thus, ACE induction by 20-HETE brings about increases in Ang II levels and its actions through the AT1R in vascular smooth muscle and endothelial cells. Such interactions may constitute, at least in part, the mechanism by which 20-HETE causes hypertension (Fig. 1).

ANDROGEN-INDUCED HYPERTENSION AND 20-HETE

The possible role of 20-HETE in androgen-induced hypertension was first introduced by investigators who undertook a genetic approach to substantiate a causal relationship between CYP4, 20-HETE, and blood pressure.^{20,41} These investigators found that targeted disruption of the Cyp4a14 gene (the mouse homologue of the rat CYP4A2) resulted in spontaneous hypertension that was androgen-dependent.²⁰ The Cyp4a14 null mice displayed increased plasma androgens, elevated expression of Cyp4a12, and increased urinary excretion of 20-HETE. Castration of male Cyp4a14 null mice normalized blood pressure, whereas administration of 5 α dihydrotestosterone (DHT) to normotensive animals increased blood pressure.^{20,32} Additional studies suggested that hypertension in the Cyp4a14 null mice is the consequence of both androgen-driven increase in salt reabsorption at the level of the

proximal tubules, a major site of 20-HETE synthesis in the kidney, and a 20-HETE–dependent increase in renal and peripheral vascular resistance.^{187–189}

The correlation between androgen and increased Cyp4a12 expression is also seen in wild-type mice. Muller et al¹⁹ compared the level of Cyp4a12a expression in male and female wild-type mice from NMRI, FVB/N, 129 Sv/J, Balb/C, and C57BL/6 backgrounds. In general, levels of Cyp4a12 were higher in males compared with that of females (45-fold for NMRI, 88-fold for FVB/N, 40-fold for 129 Sv/J, 7-fold for Balb/c, and 48-fold for C57BL/6). These results correlated with 20-HETE production in mouse renal microsomes in which males had higher levels than female mice. Along with sex differences, exogenous implantation of a pellet containing 5 α -DHT (5 mg/d pellet) led to further increases in Cyp4a12 expression and microsomal 20-HETE production. In addition to this mouse model, exogenous androgen increased 20-HETE production and blood pressure in rats. Both male and female Sprague Dawley rats treated with DHT were found to have elevated blood pressure and increased 20-HETE production in renal microvessels.^{32,42} This effect was mediated through the androgen receptor.² RNA analysis from whole kidney and renal interlobar arteries showed that DHT elevated the expression of CYP4A8 (the rat homologue to the mice Cyp4a12).³² Further, inhibition of 20-HETE synthesis with HET0016 attenuated androgen-mediated blood pressure elevation, showing that androgen-dependent hypertension is 20-HETE–mediated.³² The CYP4F2 transgenic mice in which the human CYP4F2 expression is driven by the kidney androgen-regulated protein promoter are also hypertensive and their blood pressure correlates with levels of urinary 20-HETE.¹⁹⁰ Administration of exogenous androgen to CYP4F2 transgenic mice aggravates hypertension, which can be attenuated by treatment with HET0016.¹⁹¹

ASSOCIATION BETWEEN CYP4 FAMILY POLYMORPHISMS AND HYPERTENSION IN HUMANS

To date, many different polymorphisms have been identified in the CYP4 family. The contribution of these polymorphisms toward manifestation of hypertension has not yet been clearly defined.¹⁹² The CYP4A11 gene is a highly polymorphic gene (Table 1), of which the most important genetic variant is T8590C. The T8590C variant has a thymidine to cytosine substitution at nucleotide 8590 in the CYP4A11, resulting in a phenylalanine to serine substitution at amino acid 434. This missense variant results in a significant reduction in the catalytic activity of CYP4A11 in vitro¹⁶; however, its role in blood pressure modulation is yet to be elucidated due to conflicting results from various cohort studies. In the Tennessee cohort,¹⁶ the 8590C allele was associated with an increased risk of hypertension in whites; however, it had no effect in African Americans. These findings were also observed in subjects from the Framingham Heart Study.¹⁶ In the African American Study of Kidney Disease in which 732 African Americans with hypertensive renal disease were screened, men with 8590CC genotype were associated with higher systolic blood and pulse pressures.¹⁹³ Other studies of different populations, such as the Swedes¹⁹⁴ and the Germans in the MONICA study,¹⁹⁵ have also shown that the carriers of the C allele had higher blood pressures and prevalence of hypertension. In a study of 32 hypertensive subjects, the 8590C allele was found to be associated with a higher aldosterone:renin ratio, higher waist:hip

ratio, and lower urinary 20-HETE in response to salt loading.¹¹² Williams et al¹⁹⁶ also found the 8590C allele to be associated with hypertension. They also showed that CC genotype was associated with SS hypertension. This could be partially related to their observation that the CC genotype was associated with a lesser increase in renal blood flow on salt-loading when compared with TC/TT genotypes. Interestingly, this observation is similar to findings in the Dahl SS rat model of hypertension.⁵⁰

Studies by other investigators have shown contrasting results. Ward et al¹¹³ found no difference in systolic or diastolic blood pressure between the TC/CC genotype and the TT genotype in the CYP4A11 gene. On the contrary, the TC and TT genotypes were significantly higher in hypertensive patients than in control subjects in a Japanese population.¹⁹⁷ Interethnic studies examining variations of CYP4A11 polymorphism were performed by Lino Cardenas et al.¹⁹⁸ The investigators compared the frequency of the T8590C allele between healthy and unrelated subjects from 5 different ethnic groups: French whites, Gabonese African, Senegalese Africans, Peruvians, and Tunisians. They found Tunisians to have the highest allele frequency, followed by Senegalese, Gabonese, and Peruvian, with the lowest being in the French population. Given that 20-HETE has opposing effects in the tubules versus the vasculature, the distribution of CYP4A11 expression within different ethnic groups may play a role in determining blood pressure regulation. In addition to the T8590C polymorphism, SNPs in the intron region of CYP4A11 have been shown to be associated with hypertension. In a study of a Chinese population, Zhang et al¹⁹⁹ found the SNP rs4660980 to be positively correlated to both systolic and diastolic blood pressure. Also, there was tight linkage disequilibrium between rs4660980 and rs1126742 (T8590C polymorphism). Functional variants in the promoter region of CYP4A11 have been found to also play a role in blood pressure regulation. Sugimoto et al²⁰⁰ observed that the wild-type -845GG genotype was associated with lower promoter activity when compared with -845AA genotype. Further, the -845G variant was positively correlated to hypertension in a Japanese population comprising 1501 subjects. Interestingly, no association between the 8590C allele and hypertension was observed in the sample population. More studies in different populations are required to further identify the contribution of novel CYP4A11 SNPs such as -845G/A and rs4660980 to hypertension.

Recent studies have also shown that in addition to CYP4A11, polymorphisms in CYP4F2, both in the regulatory region and in the coding region, are associated with hypertension (Table 2). Studies by Liu et al^{201,202} showed that G421C (c. -48G→C, rs3093100) in the regulatory region of the CYP4F2 gene is correlated with essential hypertension. Further investigation identified 6 additional variants in the regulatory region of CYP4F2: c. -91T→C (rs3093098), c. -77T→C (rs3093099), c. -43C→T (rs3093101), c. -23G→A (rs3093102), c. -13T→C (rs3093103), and c. +34T→G (Trp12Gly, rs3093105) within intron 1 and exon 2. These polymorphisms commonly made up 2 haplotypes, Hap 1 (c. -91T/c. -48G/c. -13T/c. +34T) and Hap II (c. -91C/c. -48C/c. -13C/c. +34G). Hap I was associated with an increased transcriptional activity of CYP4F2 via increased NF-κB binding to the c. -91T→C variant, resulting in elevated urinary 20-HETE levels. This increase in urinary 20-HETE was associated with hypertension in both the case-control and family-based studies. Interestingly, levels of urinary 20-HETE were slightly higher in men than in women.²⁰²

Stec et al²⁰³ further identified 2 nonsynonymous SNPs that led to amino acid changes at position 12 (W12G) and 433 (V433M) in African and European Americans (n = 24 and n = 23, respectively). The valine-to-methionine amino acid substitution at 433 was the result of a guanine-to-adenine missense transition at nucleotide 1347 (rs2108622). The M433 amino acid change was associated with a reduced catalytic activity; the recombinant M433 mutated CYP4F2 protein demonstrated a 56–66% decrease in its ability to convert arachidonic acid to 20-HETE.²⁰³ However, other studies that are discussed below have shown associations between V433M polymorphism and increased urinary 20-HETE and hypertension.

Ward et al¹¹³ performed a study on 235 individuals and found that in the CYP4F2 coding region, 50% were homozygous for the G allele (GG), 40% were heterozygous with a single A transition (GA), and 9% were homozygous for the A allele (AA). Individuals with either GA or AA had significantly higher blood pressure than those with the GG alleles. Further, patients with the GA or AA alleles also had the highest levels of urinary 20-HETE. Similar findings were confirmed by Fava et al¹⁹⁴ in a cohort of the Malmö Diet and Cancer Study where it was found that the V433M polymorphism in CYP4F2 is associated with elevated blood pressure and an increase in hypertension prevalence in the male urban population-based sample of middle-aged Swedes. A case-control study in an Indian population by Munshi et al²⁰⁴ also found that the GA or AA genotype was associated with hypertension. Recent studies by Hu et al²⁰⁵ showed that patients with either the M433M or V433M polymorphism had elevated urinary 20-HETE concentrations compared with that of V433V homozygotes. Also, M433 allele carriers had a significantly greater peripheral augmentation index in men versus that in V433V homozygotes, suggesting that 20-HETE may play a role in modulating arterial stiffness, contributing to hypertension. Fava et al²⁰⁶ further illustrated that M433M and V433M resulted in increased susceptibility to hypertension and/or stroke in an androgen-dependent and a sexual dimorphic manner. Although V433M has a decreased catalytic activity, multiple studies have shown that patients with this mutation present with elevated urinary 20-HETE and blood pressure. This phenomenon may be similar to observations seen in the Cyp4a14 knockout mice in which a decreased Cyp4a14 expression and function led to an increase in Cyp4a12 expression and 20-HETE production.²⁰ It is possible to conceive that a decrease in CYP4F2 function in the V433M variant may lead to an increase in expression of an alternative 20-HETE-producing ω -hydroxylase.

Fu et al²⁰⁷ showed that along with SNPs found in the coding region, CC genotype of the SNP rs155139 found in the intron region of CYP4F2 is associated with hypertension when compared with the CT/TT genotypes. Interestingly, no significant difference in prevalence of hypertension was seen in GG or GA/AA genotypes in V433M polymorphisms.²⁰⁷ Given the complex nature of CYP4 family polymorphisms and hypertension, more population-based studies are needed to identify the role of CYP4A11 and CYP4F2, the 2 major 20-HETE-producing enzymes, in the regulation of blood pressure in humans.

Several of the association studies indicated sex-specific effects of genetic variants on 20-HETE levels and/or blood pressure, suggesting that these variants, at least in part, contribute to sexual dimorphism in blood pressure. Sex-specific differences in arterial blood pressure have been well documented in epidemiological, clinical, and experimental studies. Men younger than 60 years have a higher systolic blood pressure than premenopausal women of

the same age.^{208–210} These sex-specific differences in blood pressure are also seen in animal models where males displayed higher blood pressure than females.^{20,211–217} Genetic polymorphism may be one of the determinants of these sex-specific differences, and androgen, which has been shown to cause hypertension in animal models^{32,41,42} and is correlated with higher blood pressure in men, postmenopausal women, abusers of anabolic-androgenic steroids, and women with polycystic ovary syndrome, as reviewed by Wu et al.² Thus, genetic polymorphism in enzymes that produce 20-HETE, coupled with the fact that androgen induces expression and synthesis of 20-HETE together with 20-HETE biological activities, may create an interplay that contributes to male-specific increases in blood pressure.

CONCLUSIONS

The role of 20-HETE in blood pressure regulation is quite complex. On the one hand, it promotes constriction and vascular dysfunction, and on the other hand, it inhibits salt reabsorption in the kidney. Hence, the specific cellular localization of overproduced or downregulated 20-HETE (eg, vascular vs renal tubular structures) significantly impact on the final outcome with regard to hypertension. Other factors that may impact on the contribution of 20-HETE to blood pressure regulation include diet-, age-, and sex-specific alterations in the expression of CYP enzymes that produce 20-HETE. Recent advancements in gene sequencing have identified multiple SNPs in both CYP4A and CYP4F families that are associated with blood pressure regulation. Further studies are needed to: (1) identify mechanisms underlying the antihypertensive/prohypertensive effects of 20-HETE; (2) determine the cellular localization of specific human CYP4A and CYP4F families; and (3) understand the role of various polymorphisms to assist in designing potential therapeutic agents that can amplify the antihypertensive effects of 20-HETE in the tubules or reverse the prohypertensive effects of 20-HETE in the microvasculature for blood pressure regulation.

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FIGURE 1.

Postulated mechanisms underlying the prohypertensive actions of 20-hydroxy-5, 8, 11, 14-eicosatetraenoic acid (20-HETE). ACE indicates angiotensin-converting enzyme; AGT, angiotensinogen; Ang II, angiotensin II; AT1R, angiotensin type 1 receptor; CYP, cytochrome P450; EC, endothelial cell; IKK, IκB kinase; Kca, calcium-activated potassium channel; NF-κB, nuclear factor-kappa B; NO, nitric oxide; O₂⁻, superoxide; VSMC, vascular smooth muscle cell.

TABLE 1

CYP4A11 Gene Polymorphisms

SNP	Gene Region	Function	Population Studied	Effect of Variant
-845 G/A	Regulatory	Promoter activity of variant -845GG was significantly lower than wild-type -845AA ²⁰⁰	Japanese (Sugimoto et al ²⁰⁰)	Associated with higher blood pressure
rs1126742/ T8590C Thymidine to cytosine substitution at nucleotide 8590 resulting in phenylalanine to serine substitution at amino acid 434	Intron	Associated with significantly reduced arachidonic acid metabolizing capacity in vitro ¹⁶ and a reduction in 20-HETE excretion in urine in humans ^{112,113}	White (Gainer et al ¹⁶) African American (Xu et al ¹⁷) African American (Gainer et al ¹⁹³) Swedish (Fava et al ¹⁹⁴) German (Mayer et al ¹⁹⁵) Mixed population of whites and blacks (Laffer et al ¹¹²) Mixed (Williams et al ¹⁹⁶) Japanese (Fu et al ¹⁹⁷) Australian (Ward et al ¹¹³) Japanese (Sugimoto et al ²⁰⁰)	Associated with hypertension No association with hypertension Higher systolic BP and pulse pressure in men; no effect seen in women Higher systolic BP in S434S homozygotes Higher systolic and diastolic blood pressures in individuals with CC genotype Higher diastolic blood pressures and diminished 20-HETE excretion in response to salt loading Associated with higher blood pressures. Salt sensitivity of blood pressure among hypertensive individuals Associated with hypertension No difference in systolic or diastolic blood pressures No association with blood pressure
rs4660980	Intron	Unknown	Chinese (Zhang et al ¹⁹⁹)	Higher systolic and diastolic blood pressure in men. Also, this SNP was in tight LD with rs1127742 (T8590C). Possible that the real association with blood pressure was due to rs1126742

20-HETE indicates 20-hydroxy-5, 8, 11, 14-eicosatetraenoic acid; BP, blood pressure; LD, linkage disequilibrium; SNP, single nucleotide polymorphism.

TABLE 2

CYP4F2 Gene Polymorphisms

SNP	Gene Region	Function	Population Studied	Effect of Variant
rs3093100/ G421C (c.-48 G→C)	Regulatory	421G variant was associated with lower promoter activity ²⁰¹	Chinese (Liu et al ²⁰¹)	Associated with hypertension
c.-91T→C, c.-77T→C, c.-43C→T, c.-23G→A, c.-13T→C and c.+34T→G, which make up 2 haplotypes Hap I (c.-91T/c.-48G/ c.-13T/ c.+34T) and Hap II (c.-91C/c.-48C/ c.-13C/ c.+34G)	Regulatory	Increased transcriptional activity via increased NF- κ B binding affinity of c.-91T→C variant in Haplotype I and elevated urinary 20-HETE ²⁰²	Chinese (Liu et al ²⁰²)	Associated with hypertension
rs2108622/c.1347G→A Guanine to adenosine missense mutation at nucleotide 1347 resulting in valine to methionine substitution at amino acid 433	Exon	Reduced arachidonic acid metabolizing capacity and decreased 20-HETE production in vitro ²⁰³ ; however, increased 20-HETE urinary excretion has been noted in multiple human studies ^{113,205}	Australian (Ward et al ¹¹³) Swedish (Fava et al ¹⁹⁴) Indians (Munshi et al ²⁰⁴) Chinese (Hu et al ²⁰⁵) Japanese (Fu et al ²⁰⁷)	Higher blood pressure in GA and AA genotype Higher systolic and diastolic blood pressures among male, but not female M433 carriers Associated with hypertension Greater peripheral and central augmentation indices and faster pulse rate No association with hypertension
rs1558139	Intron	Unknown	Japanese (Fu et al ²⁰⁷)	CC genotype of the variant was associated with essential hypertension when compared with CT/TT genotypes in males

20-HETE indicates 20-hydroxy-5, 8, 11, 14-eicosatetraenoic acid; NF- κ B, nuclear factor-kappa B; SNP, single nucleotide polymorphism.