Abnormal Pressure–Natriuresis in Hypertension: Role of Cytochrome P450 Metabolites of Arachidonic Acid

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The pressure–natriuresis relationship is shifted to higher pressures in genetic and experimental models of hypertension; however, the factors responsible for altering kidney function remain to be determined. In spontaneously hypertensive (SHR) and Lyon hypertensive rats, the resetting of pressure–natriuresis results from increased preglomerular renal vascular tone, whereas sodium reabsorption is elevated in the thick ascending loop of Henle (TALH) of Dahl S rats. Recently, a new route for the renal metabolism of arachidonic acid (AA) has been described, and there is evidence that this pathway contributes to the resetting of renal function in hypertension. In the kidney, cytochrome P450 (CYP) enzymes metabolize AA primarily to 20-HETE and EETs. 20-HETE is a potent constrictor of renal arterioles that has an important role in autoregulation of renal blood flow and tubuloglomerular feedback. 20-HETE and EETs also inhibit sodium reabsorption in the proximal tubule and TALH. In the SHR, the renal production of 20-HETE is elevated and inhibitors of the formation of 20-HETE decrease arterial pressure. Blockade of 20-HETE formation also reduces blood pressure or improves renal function in deoxycorticosterone acetate (DOCA)-salt, angiotensin II--infused, and Lyon hypertensive rats. In contrast, 20-HETE formation is reduced in the TALH of Dahl S rats and this contributes to elevated sodium reabsorption. Induction of 20-HETE synthesis improves pressure–natriuresis and lowers blood pressure in Dahl S rats, whereas inhibitors of the synthesis of 20-HETE promote the development of hypertension in Lewis rats. These findings indicate that the renal production of CYP metabolites of AA is altered in genetic and experimental models of hypertension and that this system contributes to the resetting of pressure–natriuresis and the development of hypertension in some models. Am J Hypertens 2001;14:90S–97S © 2001 American Journal of Hypertension, Ltd.

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of hypertension and the genes involved remain to be determined.

Three lines of evidence emerged 10 years ago that suggest that cytochrome P450 (CYP) metabolites of arachidonic acid (AA) might be involved in the development of hypertension. First, Iwai and Inagami identified the CYP4A2 gene along with the Sa gene as one of three genes that were preferentially overexpressed in the kidney during the development of hypertension in SHR. Considerable work was done to test the role of the Sa gene in the development of hypertension but the CYP4A2 gene was largely ignored. Second, McGiff and Schwartzman’s groups reported that the production of 20-hydroxyeicosatetraenoic acid (20-HETE) was elevated in the kidney of SHR. Finally, several investigators reported that administration of SnCl2 and heme arginate lowered the renal synthesis of 20-HETE and blood pressure in SHR. These seminal observations provided the rationale for exploring the role of CYP metabolites of AA in the regulation of renal function, vascular tone, and the long-term control of arterial pressure.

Renal Metabolism of AA

Arachidonic acid is primarily metabolized in the kidney by CYP pathways to epoxyeicosatrienoic acids (EET), dihydroxyeicosatetraenoic acids (DiHETE), and 20-HETE. The formation of 20-HETE is catalyzed by CYP enzymes of the 4A family. Four isoforms, 4A1, 4A2, 4A3, and 4A8, have been cloned from the kidneys of rats. All of these isoforms except CYP4A8 produce 20-HETE when incubated with AA. Using reverse transcriptase–polymerase chain reaction (RT-PCR) and Western blot techniques, we demonstrated that CYP4A2 and 4A3 mRNA and protein are highly expressed in renal arterioles, glomeruli, proximal tubules, and TALH microdissected from the kidneys of rats. CYP4A8 is expressed in the cortical proximal tubule, cortical thick ascending loop of Henle, and the cortical collecting duct. Interestingly, CYP4A8 is not expressed in any medullary structures. CYP4A1 mRNA levels are extremely low and cannot be detected by RT-PCR in microdissected vessels or tubules. It can be detected at the whole kidney level only when microgram quantities of RNA are reverse transcribed. The issue of which isoform is most important to the production of 20-HETE in the kidney, however, is still unresolved because the catalytic activity of CYP4A1 is tenfold higher than that of CYP4A2 or 4A3.

Many factors influence the expression of CYP4A enzymes. CYP4A1 and 4A3 protein are highly expressed in the kidney of neonatal rats but the levels decline in adulthood. CYP4A2 is the primary isoform expressed in the kidney of adult male rats. Fibrates interact with the PPAR receptor to induce the expression of CYP4A1 and 4A3 in the liver and kidney and promote the synthesis of 20-HETE. Angiotensin II (Ang II), vasopressin, and endothelin increase the synthesis of 20-HETE, which contributes to the vasoconstrictor response to these agonists. The renal metabolism of AA through CYP enzymes is altered in diabetes, pregnancy, hepatorenal syndrome, and cyclosporin-induced nephrotoxicity, and in various models of hypertension. However, a role for 20-HETE in mediating the changes in renal function associated with these conditions has yet to be established.

P450 Metabolites of AA in the Control of Renal Vascular Tone

Renal arterioles produce EET and 20-HETE when incubated with AA. EET are produced by the endothelium and are potent vasodilators. They hyperpolarize renal vascular smooth-muscle (VSM) cells by increasing the activity of a large conductance, Ca2+-activated potassium (KCa) channel. Thus, EET have been suggested to be an endothelial-derived hyperpolarizing factor (EDHF).

We have reported that 20-HETE is a potent constrictor (EC50<10^-8 M) of renal and cerebral arterioles. It promotes Ca2+ entry by depolarizing VSM cells secondary to blockade of the KCa channel and increases the conductance of L-type Ca2+ channels. Inhibitors of the formation of 20-HETE activate the KCa channel and increase the conductance of L-type Ca2+ channels. Inhibitors of the formation of 20-HETE block the myogenic response of renal arterioles to elevations in transmural pressure in vitro and auto-regulation of renal blood flow (RBF) in vivo.

Given the central role of 20-HETE in the regulation of renal vascular tone, considerable effort has been focused on delineating the interactions of 20-HETE with Ang II, NO, and other major systems that influence renal hemodynamics. Recent studies indicate that Ang II, endothelin, and other vasoconstrictors stimulate the release of AA and formation of 20-HETE in renal VSM cells by raising the intracellular Ca2+ concentration and activating phospholipase A2. 20-HETE then prevents activation of KCa channels that normally accompany an increase in intracellular Ca2+ concentration. This prevents hyperpolarization of the cell and facilitates Ca2+ entry through voltage-sensitive Ca2+ channels. In support of this hypothesis, several investigators have found that inhibitors of 20-HETE formation attenuate the renal vasoconstrictor responses to vasopressin, Ang II, and endothelin. In the case of endothelin, Imig et al also reported that whereas blockade of 20-HETE formation has no effect on the initial rise in intracellular Ca2+ concentration in renal VSM cells, it markedly attenuates the sustained elevation in intracellular Ca2+ concentration that is dependent on Ca2+ influx through voltage-sensitive channels. Our laboratory has obtained similar results with Ang II.

20-HETE also plays an important role in mediating the cyclic guanosine monophosphate (cGMP)-independent component of the vasodilator response to NO and CO in renal
arterioles and vessels from other vascular beds. In this regard, we have shown that NO, like CO, binds to the heme in the CYP4A enzyme and inhibits the formation of 20-HETE.\(^{33,34}\) Moreover, in renal and cerebral arteries the fall in 20-HETE levels after administration of NO mediates activation of K\(_{Ca}\) channels and between 50% and 75% of its vasodilator response.\(^{33-35}\) The remainder of the vasodilator response to NO is independent of K\(^+\) channels because it cannot be blocked by high K\(^+\) media or K\(^+\) channel blockers.\(^{35}\) The residual response to NO is also cGMP dependent because it can be blocked by guanylyl cyclase inhibitors and appears to be mediated by desensitization of the contractile mechanism to intracellular Ca\(^{2+}\). At the level of the intact animal, inhibition of the formation of 20-HETE blocks the vasodilator response to NO donors and attenuates the rise in arterial pressure, fall in RBF, and natriuretic effects of inhibitors of NO synthase.\(^{33,36}\)

20-HETE also participates as a mediator/modulator of tubuloglomerular feedback (TGF) responses in the kidney.\(^{37}\) In this regard, the enzyme responsible for the formation of 20-HETE is expressed in the Macula densa and 20-HETE is a potent constrictor of the afferent arteriole.\(^{23,27}\) Perfusion of the loop of Henle with AA potentiates, whereas CYP inhibitors block TGF responses.\(^{37}\) Addition of 20-HETE to the tubular perfusate restores TGF feedback responses after inhibition of endogenous 20-HETE production.\(^{37}\) These studies suggest that 20-HETE either serves as the mediator of TGF, or acts as a second messenger at the level of the afferent arteriole to transduce the response to other mediators released by the Macula densa. The idea that 20-HETE serves as a mediator or modulator of TGF is also consistent with the known effects of NO and Ang II on TGF. In this regard, NO blocks 20-HETE production\(^{33,34}\) and attenuates TGF response,\(^{38}\) whereas Ang II stimulates 20-HETE production\(^{18,32}\) and potentiates the sensitivity of TGF.\(^{39}\)

CYP4A protein is also expressed in pericytes surrounding vasa recta capillaries.\(^{14}\) This latter finding is consistent with previous observations that inhibitors of 20-HETE formation selectively increase renal medullary blood flow.\(^{40}\) 20-HETE may also contribute to the actions of other mediators on intrarenal distribution of blood flow. In this regard, Hercule and Oyekan\(^{41}\) recently reported that endothelin increases medullary blood flow while reducing renal cortical blood flow and that inhibition of NO or 20-HETE production attenuates the increase in medullary blood flow. They concluded that endothelin raises medullary blood flow by increasing the production of NO, which then blocks the formation of the vasoconstrictor 20-HETE.

### P450 Eicosanoids and the Regulation of Sodium Transport

CYP metabolites of AA also play an important role in the regulation of tubular reabsorption in the kidney. 20-HETE is the primary metabolite of AA produced by the proximal tubule, where it inhibits Na\(^+\)-K\(^+\)-ATPase activity.\(^{42}\) Quigley et al\(^{43}\) recently demonstrated that 20-HETE inhibits sodium transport in isolated perfused rabbit proximal tubules and that perfusion of the tubules with 19-HETE has the opposite effect. This latter finding is interesting because Alonso-Galicia et al\(^{44}\) recently reported that 19-HETE is a competitive antagonist of 20-HETE action. Thus, the stimulatory effect of 19-HETE on proximal sodium reabsorption may be due to blockade of the action of endogenously produced 20-HETE. Other studies have shown that the inhibitory effects of parathyroid hormone (PTH), dopamine, and Ang II on Na\(^+\)-K\(^+\)-ATPase activity and sodium transport in the proximal tubule are dependent on the formation of 20-HETE and/or EET.\(^{45-48}\) Recent work by Nowicki et al\(^{48}\) indicated that 20-HETE stimulates protein kinase C (PKC) to phosphorylate and inhibit Na\(^+\)-K\(^+\)-ATPase. 20-HETE and EET may also affect Na\(^+\) transport in the proximal tubule by influencing the translocation of the NH3 Na\(^+\)-H\(^+\) exchanger to the apical membrane.\(^{36,47}\) These findings suggest that 20-HETE has an important role in the control of sodium excretion and thereby may influence pressure–natriuresis and long-term control of arterial pressure. In this regard, Zhang et al\(^{47}\) recently reported direct involvement of CYP metabolites of AA in mediating the pressure–natriuresis response. They found that pretreatment of rats with CoCl\(_2\), which inhibits formation of EET and 20-HETE, blocks the inhibitory effects of elevations in renal perfusion pressure on Na\(^+\)-K\(^+\)-ATPase activity, the redistribution of NHE-3 to the apical membrane and proximal tubule sodium transport.

20-HETE also has a critical role in the regulation of Cl\(^-\) transport in the TALH. Escalante et al\(^{49}\) and Carroll et al\(^{50}\) first reported that 20-HETE was the primary metabolite of AA produced in TALH cells and that it inhibited Na\(^+\)-K\(^+\)-2Cl\(^-\) transport. Subsequent patch clamp studies by Wang and Lu\(^{31}\) revealed that 20-HETE blocks a 70-pS K\(^+\) channel in the apical membrane of the TALH cells. Blockade of this channel limits K\(^+\) availability for transport through the Na\(^+\)-K\(^+\)-2Cl\(^-\) transporter and reduces the lumen positive transepithelial potential that serves as the driving force for passive reabsorption of cations in the TALH. Our recent finding that CYP4A inhibitors increase and 20-HETE decreases transepithelial voltage and Cl\(^-\) transport in the isolated TALH of the rat supports this view.\(^{5}\) Others have also reported that the inhibitory effects of Ang II, bradykinin, and elevations in intracellular Ca\(^{2+}\) on sodium transport in the TALH can be blocked by CYP inhibitors and are mediated by 20-HETE.\(^{22}\) In addition, evidence suggests that the effects of NO\(^5\) and CO\(^5\) on K\(^+\) channel activity and sodium transport in the TALH may be linked to inhibition of the formation of 20-HETE.

### Role of P450 Metabolites of AA in Hypertension

Given the importance of 20-HETE in the regulation of renal and peripheral vascular tone and the renal handling of sodium, there has been considerable interest in exploring the role of this pathway in hypertension. There is now

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unequivocal evidence that the renal production of 20-HETE and EET is altered in many models of hypertension and that blockade of this pathway alters blood pressure in several of these models. However, it is still difficult to predict the consequences of blockade of this pathway on blood pressure, because it has both pro- and antihypertensive properties. At the level of the renal tubule, 20-HETE and EET inhibit sodium transport and oppose the development of hypertension. However, in the renal and peripher al vasculature, 20-HETE is a potent vasoconstrictor that promotes hypertension. On the other hand, EET are endothelial-derived vasodilators that have antihypertensive properties. This issue is further complicated because all the inhibitors (COCl₂, SnCl₂, ABT, 17-ODYA, miconazole, and ketoconazole) that have been used in previous long-term studies are not selective at inhibiting the formation of EET vs 20-HETE. More selective inhibitors of the formation of 20-HETE (DDMS and DBDD) and EET (PPOH and PPOMS) are now available. However, these drugs have not been used in long-term studies. Moreover, the efficacy of these drugs in vivo remains to be established because they are reversible inhibitors and they bind to plasma proteins and are poorly filtered by the kidney.

**CYP Metabolites of AA in Experimental Models of Hypertension**

**DOCA-Salt Hypertension**

Recent studies indicate that endothelin stimulates the release of 20-HETE and that 20-HETE has a role in mediating the vasoconstrictor and natriuretic actions of endothelin in the kidney. More recently, Oyekan et al. examined the effects of inhibiting the formation of 20-HETE on the development of hypertension and end-organ damage in DOCA-salt hypertension in rats. This model is characterized by elevations in plasma endothelin levels, and endothelin receptor antagonists reduce blood pressure and renal and vascular injury. DOCA-salt treatment produced a fourfold elevation in the renal excretion of endothelin and 20-HETE in rats. Long-term administration of CoCl₂ to induce heme oxygenase activity and lower renal 20-HETE production reduced blood pressure in rats treated with DOCA and salt from 193 ± 6 to 157 ± 7 mm Hg. CoCl₂ treatment also minimized vascular damage, renal injury and proteinuria in these rats. To help resolve the role of elevations in CO vs inhibition of CYP activity in the antihypertensive effects of CoCl₂, experiments were also performed using 1-aminobenzotriazole (ABT), which is a more specific inhibitor of the renal synthesis of 20-HETE and EET. ABT also prevented the development of hypertension in DOCA-salt-treated rats. However, it did not reduce the degree of renal hypertrophy and proteinuria. These studies indicate that 20-HETE, presumably acting to potentiate the vasoconstrictor actions of endothelin at the level of the renal and peripheral vasculature, contributes to the development of DOCA-salt hypertension.

In contrast, Honeck et al. recently reported that 20-HETE production is reduced rather than elevated in DOCA-salt hypertensive mice and that treatment of these mice with fibrates to induce the renal formation of 20-HETE prevented the development of hypertension. Thus, the role of CYP eicosanoids as pro- or antihypertensive factors in DOCA-salt hypertension remains unresolved.

**Ang II-Induced Hypertension**

A similar story has emerged regarding the role of CYP metabolites of AA in the development of hypertension in rats infused with Ang II. Ang II stimulates the formation of 20-HETE in rat renal microvessels and in the isolated perfused rabbit kidney. We have found that blockade of 20-HETE formation attenuates the vasoconstrictor actions of Ang II in isolated renal arteries in vitro and the transient pressor response to intravenous infusion of Ang II in rats in vivo. These findings suggest that elevations in vascular 20-HETE production may contribute to the development of Ang II–induced hypertension. On the other hand, CYP metabolites of AA also mediate the inhibitory effects of Ang II on sodium transport in the proximal tubule and TALH. Based on these findings, blockade of 20-HETE would be expected to promote sodium retention and potentiate the hypertensive actions of Ang II. In an attempt to resolve this dilemma, Muthalif et al. recently examined the role of CYP metabolites of AA in the development of hypertension in rats infused with Ang II. They found that chronic blockade of the renal formation of EETs and 20-HETE with ABT reduced blood pressure from 171 ± 3 to 113 ± 8 in rats infused with Ang II. We have also confirmed that chronic administration of ABT or DDMS, a more selective inhibitor of 20-HETE synthesis, attenuates the development of Ang II–induced hypertension in rats. The mechanism by which these drugs attenuate the rise in blood pressure in the Ang II model of hypertension remains unclear. For DDMS, it is likely that this compound is poorly filtered and it may not inhibit tubular CYP4A activity and only blocks 20-HETE production in the vasculature. On the other hand, ABT does block synthesis of EET and 20-HETE in the kidney. This should enhance sodium reabsorption and oppose its antihypertensive actions on vascular tone. Thus, it may be that other mechanisms for the control of sodium excretion compensate for the loss of 20-HETE in the kidney and only the vascular effects of ABT predominate. Further work in this area is required to answer these questions.

**CYP Metabolites of AA in Genetic Models of Hypertension**

**SHR**

Numerous investigators have reported that the expression of CYP4A protein and 20-HETE production is elevated in the kidney of SHR. Moreover, administration of inducers of heme oxygenase that lower the synthesis of
20-HETE prevent the development of hypertension in SHR.11,12 Because 20-HETE is a potent renal vasoconstrictor, we suggested that 20-HETE contributes to resetting of the pressure–natriuresis relationship in SHR by elevating renal vascular resistance and TGF responses.58 In support of this view, we found that inhibitors of 20-HETE formation normalize the elevated renal vascular resistance in the kidneys of SHR.58

Still, the contribution of CYP metabolites of AA to the development of hypertension in SHR remains unsettled for several reasons. First, the relative importance of elevations in CO production v inhibition of 20-HETE formation in mediating the antihypertensive effects of inducers of heme oxygenase needs to be resolved. Second, the elevated renal production of 20-HETE in SHR is due to enhanced expression of CYP4A protein in proximal tubules.10 This should inhibit sodium transport and oppose rather than promote the development of hypertension. Finally, Shatara et al59 found that induction of the renal formation of 20-HETE with fibrates increases sodium excretion and attenuates the development of hypertension in SHR. Thus, the mechanism by which elevations in the renal formation of 20-HETE contribute to the development of hypertension in SHR remains unclear, unless the vasoconstrictor effects of 20-HETE overcome its tubular actions.

To test directly whether mutations in CYP4A genes have a causal role in the development of hypertension in SHR, we performed a genetic cosegregation analysis in an F2 cross of SHR and Brown Norway (BN) rats.60 We found that the CYP4A genotype had no influence on mean arterial pressure in this cross. Mean arterial pressure averaged 122 ± 1 mm Hg in the F2 rats homozygous for the SHR CYP4A alleles, 125 ± 1 mm Hg in heterozygotes, and 123 ± 2 mm Hg in rats homozygous for the BN alleles. However, the CYP4A genotype did cosegregate with the change in blood pressure (salt sensitivity) seen in the rats after they were fed a high-salt diet for 1 week.60 These findings indicate that inherited mutations in the CYP4A gene are not a primary cause of hypertension in SHR, but may contribute to the strain differences in salt sensitivity of blood pressure. These results also suggest that upregulation of renal 20-HETE production in SHR is probably related to strain differences in the neural and humoral background and that 20-HETE secondarily contributes to the elevation in vascular tone in SHR.

**Lyon Hypertensive Rats**

Recent studies evaluated the contribution of CYP metabolites of AA in altering renal function in hypertensive (LH) rats. These rats resemble SHR in that the pressure–natriuresis relationship is shifted to higher pressures and this is associated with enhanced preglomerular vascular tone that lowers renal blood flow and GFR.61,62 Intrarenal infusion of different CYP inhibitors, 17-ODYA and miconazole, enhances the pressure–natriuresis relationship and increases RBF in LH rats.61,62 Blockade of the renal formation of EET or 20-HETE has no significant effect on renal function in the Lyon normotensive strain of rats. The production of 20-HETE is lower in the kidney of LH rats relative to that seen in normotensive strains, so an excess production of this compound is not mediating the renal vasoconstriction. Moreover, the vasodilator effects of blockade of CYP in LH rats can be prevented with cyclooxygenase (COX) inhibitors and thromboxane receptor antagonists.61,62 These observations led to the idea that CYP metabolites of AA may be converted by COX-2 to thromboxane and endoperoxides and these products may mediate renal vasoconstriction and contribute to the development of hypertension in LH rats.

**Dahl S Rats**

Many laboratories, including ours, have shown that the pressure–natriuresis relation is shifted in Dahl S rats so that the kidney requires a higher perfusion pressure to excrete the same amount of sodium as normotensive rats.63 Micropuncture and in vivo and in vitro tubular microperfusion experiments demonstrated that this is due to elevated Cl- transport in the TALH.7,8 Given the evidence that 20-HETE serves as one of the major endogenous regulators of Cl- transport in the TALH,69,70 we studied whether production of this substance is altered in Dahl S rats. We found that the production of 20-HETE and expression of CYP4A protein are reduced in Dahl S rats relative to Dahl R64 and other normotensive strains.65 and postulated that a deficiency in the formation of 20-HETE may lead to an elevation in Cl- transport and development of salt-sensitive hypertension. Along these lines, Makita et al66 suggested that a deficiency in EET production might also contribute to the development of hypertension in the Dahl S rat, as they found that elevations in salt intake increase the production of EET in normotensive strains of rats but not in Dahl S rats.

To determine whether a deficiency in the formation of 20-HETE might contribute to the development of hypertension in Dahl S rats, a genetic cosegregation study was performed.65 We developed a genetic marker spanning a repeated element in intron 11 of the CYP4A2 gene, mapped this locus to rat chromosome 5, and used it to genotype 151 F2 rats derived from a cross of Dahl S and Lewis rats. The CYP4A2 genotype strongly cosegregated with blood pressure in this population.65 Systolic blood pressure averaged 201 ± 6 mm Hg in rats with the SS genotype, 192 ± 4 mm Hg in heterozygotes, and 169 ± 3 mm Hg in rats with the LL genotype. More recently, we have confirmed that transferring the region of chromosome 5 that contains the CYP4A alleles from Lewis rats into a congenic strain of Dahl S rats reduces blood pressure by about 20 mm Hg relative to that seen in the parental Dahl S rats.67

We also directly studied whether a deficiency in the formation of 20-HETE production contributes to the ele-
viation in Cl\textsuperscript{−} transport in the TALH of Dahl S rats. We found that transepithelial potential is elevated in the isolated perfused TALH microdissected from the kidneys of Dahl S rats and it reabsors more Cl\textsuperscript{−} than TALH obtained from Dahl R, Lewis, or SD rats.\textsuperscript{8} Exogenous administration of 20-HETE normalizes Cl\textsuperscript{−} transport in TALH of Dahl S rats, which are deficient in the expression of CYP4A protein, but it has no effect on Cl\textsuperscript{−} transport in the TALH of salt-resistant strains of rats.\textsuperscript{8} Inhibitors of the formation of 20-HETE increase Cl\textsuperscript{−} transport and transepithelial potential in the TALH of normotensive rats, but they have no effect in Dahl S rats. These findings were the first to indicate that 20-HETE regulates Cl\textsuperscript{−} transport in TALH of the rat, and strongly support our hypothesis that a deficiency in the formation of this substance contributes to the elevation in Cl\textsuperscript{−} transport in Dahl S rats.

Studies have also been performed to determine whether altering the levels of 20-HETE in the kidney could change arterial pressure in rats. These studies indicate that induction of the expression of CYP4A protein in the kidney with fibrates normalizes the pressure–natriuretic relationship\textsuperscript{68} and prevents the development of hypertension\textsuperscript{69,70} in Dahl S rats. It also reduces the degree of glomerular injury and proteinuria, and improves GFR in this model of hypertension.\textsuperscript{70} In other studies, chronic renal medullary infusion of an inhibitor of the formation of 20-HETE increased mean arterial pressure from 115 ± 2 to 142 ± 2 mm Hg in Lewis rats fed a high-salt diet.\textsuperscript{71} 17-ODYA reduced the synthesis of 20-HETE in the renal outer medulla of the Lewis rats to the same level seen in Dahl S rats.\textsuperscript{71} It had no effect on the production of 20-HETE in the renal cortex. These results confirm that long-term reduction in the synthesis of 20-HETE in the outer medulla of the kidney can induce salt-sensitive hypertension in normotensive rats and that elevations in renal 20-HETE production improve renal function and prevent the development of hypertension in Dahl S rats. It still remains to be determined whether a mutation in one of the CYP4A genes is responsible for the differential expression of this system in the kidney of Dahl S rats and whether 20-HETE plays a causal role in altering renal function and the development of hypertension in this strain.

CYP Metabolites of AA in Human Hypertension

There is one report that elevations in salt intake increases 20-HETE excretion in humans and that the rise in 20-HETE levels is blunted in salt-sensitive hypertensive patients.\textsuperscript{72} This observation is consistent with the results in Dahl S rats indicating that a deficiency in 20-HETE production may contribute to the development of salt-sensitive forms of hypertension.\textsuperscript{67–70}

There are also data indicating that the excretion of EET is altered in women with toxemia of pregnancy.\textsuperscript{73} Overall, little is known about the role of CYP metabolites of AA in the control of blood pressure in humans. However, given the observations in animal studies, research in this area should be pursued.

Conclusions

The role of CYP metabolites of AA in the control of renal function, vascular tone, and the long-term control of arterial pressure is a rapidly evolving field, but at present some general concepts have emerged. First, the renal, cerebral, splanchic, pulmonary, and muscle microcirculations produce 20-HETE and EET and these substances have an important role in the regulation of vascular tone by regulating K\textsuperscript{+} channel activity. 20-HETE and EET also have an important role as second messengers in the regulation of sodium reabsorption in the proximal tubule and TALH. The renal formation of 20-HETE and EET is altered in many forms of hypertension. Given the important role of 20-HETE and EET in the regulation of renal function and vascular tone, it is likely that these changes influence blood pressure. Recent studies indicate that inhibitors of the formation of 20-HETE and EET attenuate the rise in blood pressure in both AII-induced and DOCA-salt hypertension models. In the SHR, changes in the renal production of 20-HETE contribute to the alterations in renal function and blood pressure, but mutations in the CYP4A genes are not a primary cause of hypertension in this model. There is also evidence that CYP metabolites of AA contribute to the resetting of renal function in LH rats. In Dahl S rats, a deficiency in the renal production of 20-HETE contributes to the elevation in Cl\textsuperscript{−} transport in the TALH. Furthermore, the CYP4A gene lies within a region of rat chromosome 5 that cosegregates with the development of hypertension; however, it remains to be established whether a mutation in the CYP4A gene plays a causal or secondary role in the development of hypertension in this model.

References


