The Role of the Cytochrome P450-Dependent Metabolites of Arachidonic Acid in Blood Pressure Regulation and Renal Function
A Review
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Arachidonic acid metabolism through the cytochrome P450-dependent monooxygenase system has been the subject of considerable research interest over the last several years. This article reviews the biological actions of the metabolites generated through this pathway and explores their role in the regulation of renal function and systemic blood pressure. Arachidonic acid is metabolized by the cytochrome P450-dependent monooxygenase system in three ways: epoxidation, resulting in the formation of 5,6-, 8,9-, 11,12-, 14,15-epoxyeicosatrienoic acids; allylic oxidation, resulting in the formation of 5,8,9,11,12,15-hydroxyeicosatetraenoic acids (HETE); and hydroxylation, resulting in the formation of 19,20-HETEs and 20-carboxyl arachidonic acid. Elements of this pathway have been localized in the kidney and several extrarenal sites. Vasodilation, vasoconstriction, inhibition of Na⁺,K⁺-ATPase, and inhibition of ion transport and modulation of cell growth have been some of the diverse physiological actions demonstrated by metabolites produced by this pathway. As a physiological correlate of these properties, considerable evidence has accumulated regarding the role of the cytochrome P450-dependent metabolites of arachidonic acid in the pathogenesis of hypertension in the spontaneously hypertensive rat. Data in humans are limited, but in small studies increased production of these metabolites has been shown in hypertensive persons. In summary, several properties of products of this “third” pathway of arachidonic acid metabolism suggest a role in cardiovascular and renal function. Additional studies are needed to precisely define the role of this pathway in human hypertension. © 1997 American Journal of Hypertension, Ltd. Am J Hypertens 1997;10:356–365

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Arachidonic acid metabolism through the cyclooxygenase and lipooxygenase pathways has been well characterized, and contributions to pathophysiology have been well established. In recent years, there has been considerable interest in the metabolism of arachidonic acid through a cytochrome P450 and NADPH-dependent monooxygenase pathway, “the third pathway,” resulting in the formation of several novel metabolites. Arachidonic acid metabolites derived from this pathway have been documented to be biologically active and have, thereby, prompted intense research interest in their...
potential role in various pathophysiologic processes. Several properties of these products such as their vasoreactivity and ability to affect ion transport suggest a potential role in the regulation of cardiovascular and renal function. The purpose of this review is to evaluate these data and explore their implications for pathogenesis of human hypertension.

Cytochrome P450 dependent metabolism of arachidonic acid involves NADPH and three types of oxidative reactions (Figure 1) have been described.\(^1\) First, olefin epoxidation gives rise to four regioisomers\(^2\),\(^3\),\(^4\),\(^5\),\(^6\),\(^7\),\(^8\),\(^9\),\(^10\) and 14,15-epoxyeicosatrienoic acids (EET), which in turn can be hydrolyzed to the corresponding dihydroxyeicosatrienoic acids (DHET) either through the specific action of epoxide hydrolase or nonspecifically. These metabolites have been shown to be endogenous constituents of rat liver, rabbit kidney, and rat hypothalamus, as well as human urine and platelets.\(^2\)\(^-\)\(^5\) Second, allylic oxidation results in the formation of hydroxyeicosatetraenoic acids (HETE).\(^5\),\(^8\),\(^9\),\(^11\),\(^12\),\(^15\)-HETEs have been identified. And third, omega and omega\(^1\) hydroxylation generates 19- and 20-HETEs. 20-HETE can be further oxidized to 20-carboxy arachidonic acid (20-COOH-AA). In rabbit renal cortical and medullary microsomes omega/omega\(^1\) oxidation is the major pathway for arachidonic acid conversion in the presence of NADPH.\(^5\) These metabolites have been implicated in the development of hypertension in the spontaneously hypertensive rat.

**FACTORS INFLUENCING CYTOCHROME P450-DEPENDENT ARACHIDONIC ACID METABOLISM**

Several agents have been shown to inhibit the cytochrome P450-dependent metabolism of arachidonic acid. The classical inhibitor used has been SKF 525A.\(^7\) Metyrapone,\(^1\) the imidazole derivatives (ketoconazole and clotrimazole)\(^9\) carbon monoxide, 7-ethoxyresorufin, and 17-octadecynoic acid (17ODYA)\(^8\) have also been shown to inhibit this pathway. The imidazole derivatives are selective inhibitors of arachidonic acid epoxygenase, and omega and omega\(^1\) hydroxylation is relatively resistant to these compounds.\(^9\) Other agents that are known inhibitors of the cyclooxygenase and lipooxygenase pathways of arachidonic acid metabolism also inhibit cytochrome P450-dependent arachidonic acid metabolism. These include indomethacin (at high doses, IC\(_{50}\) 70 \(\mu\)mol / L) eicosatrynoic acid (ETYA, a tetracylenic analog of arachidonic acid) and nordihydroguaiaretic acid (NDGA).\(^9\) Metabolism of arachidonic acid through the cytochrome P450-dependent pathway has been shown to be influenced by several other factors. Arginine vasopressin and salmon calcitonin have been shown to stimulate the cytochrome P450-dependent arachidonic acid metabolism in cells isolated from the rabbit thick ascending loop of Henle segment via cyclic AMP mediated metabolism.\(^20\) 5,6-EET may be involved in mediating vasopressin induced calcium mobilization in A7r5 vascular smooth muscle cells.\(^11\) Interestingly, specificity of hormonal stimulation of epoxygenase versus hydroxylase activity has been demonstrated in the renal epithelium. Although angiotensin II increase EET production in proximal tubular cells,\(^12\) epidermal growth factor and parathyroid hormone increase omega-hydroxylase activity.\(^13\) This suggests that differential signal transduction mechanisms (for example, phospholipase A\(_2\) versus phospholipase C) or orientation of receptors in polarized cells may influence the P450 isozymes that metabolize arachidonic acid.

Several chemicals and drugs including phenobarbital,\(^14\) tin,\(^15\) the imidazoles,\(^9\) and general anesthetics\(^16\) have been shown to modulate cytochrome P450 monooxygenase activity. Interestingly, cyclosporine A\(^17\),\(^18\) has been shown to stimulate omega hydroxylation of arachidonic acid. Because the products of this pathway are potent vasoconstrictors, this raises the possibility of their involvement in cyclosporine nephrotoxicity. In streptozocin-induced diabetes mellitus in experimental animals, marked induction of the cytochrome P450 arachidonic acid oxygenase was demonstrated in the renal microsomes which was reversible by treatment with insulin.\(^19\) Unfortunately, there have been no studies to date in genetic animal models of diabetes.

Renal cytochrome P450-dependent monooxygenase activity can be stimulated by treatment with either glucocorticoids or mineralocorticoids.\(^8\),\(^9\),\(^20\),\(^21\) In a series of experiments, Lapuerta et al\(^22\) showed that the production of cytochrome P450 arachidonic acid products, especially 19,20-HETE in rabbit cortical and medullary microsomes, was significantly reduced following adrenalectomy and associated with a negative sodium balance. When deoxycorticosterone acetate

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**FIGURE 1.** Metabolism of arachidonic acid through the cytochrome P450 dependent pathway.
It has been suggested that the cytochrome P450 pathway may mediate the effects of adrenal steroids on renal blood flow and glomerular filtration rate (GFR). Sessa et al demonstrated that when rabbits were treated with dexamethasone, prostacyclin and PGE2 induced vasodilatation was attenuated and converted to vasoconstriction. They hypothesized that this could be secondary to induction of cytochrome P450-dependent monoxygenase activity that results in transformation of prostanoids to omega-1 and omega-2 hydroxylated products.

Van Voorhis et al explored the role of the EET in human luteinized granulosa cells and found that human chorionic gonadotropin stimulates production of EET in granulosa cells. Although further research is needed in this area, a potential role for these metabolites in regulating ovarian granulosa cell estrogen synthesis was suggested by this study. Thus, many factors have been shown to affect arachidonic acid metabolism through this pathway. Further data regarding the physiologic actions of this pathway are reviewed below.

**LOCALIZATION OF CYTOCHROME P450-DEPENDENT ARACHIDONIC ACID METABOLISM**

In the kidney, cytochrome P450-dependent metabolism of arachidonic acid has been demonstrated in several sites. After initial localization in the medullary thick ascending loop of Henle (mTALH) cells, proximal tubular cells, pars recta, cortical collecting duct, isolated glomeruli, and mesangial cells have shown cytochrome P450-dependent metabolism of arachidonic acid. However, rates of production of the different metabolites appear to be segmentally localized, with maximal production of 19- and 20-HETE seen in the proximal tubule. Maximal activity for dihdroxyeicosatetraenoic acid (DHET) and 20-carboxyl-arachidonic acid (20-COOH-AA) was found in the medullary collecting tubules. Given its property as a vasoconstrictor, it is interesting to note that 20-HETE production is maximal in the nephron segment that has most direct access to the systemic circulation and may contribute to regulation of renovascular tone.

Cytochrome P450-dependent metabolism of arachidonic acid has also been demonstrated in a variety of other tissues. The cornea has been extensively studied due to its similarity in transport characteristics with tubular epithelium, and metabolism of arachidonic acid through this pathway has been described. Cytochrome P450-dependent metabolites have also been described in ciliary body and retinal pigment epithelium, human epidermal cells, isolated pancreatic islets, guinea pig lung, rat intestine, rabbit olfactory epithelium, rat brain, and human hematopoietic tissue. Other actions attributed to these metabolites include inhibition of platelet aggregation, release of luteinizing hormone, and somatostatin. The roles of these metabolites in these locations need further clarification.

**FUNCTIONAL ROLE OF THE CYTOCHROME P450-DEPENDENT METABOLITES**

**Vascular Actions** The cytochrome P450-dependent metabolites of arachidonic acid have been shown to affect vascular reactivity in a variety of locations. The EET have been shown to vasodilate intestinal arterioles, preconstricted (indomethacin treated) renal microvessels, cerebral microvessels, rabbit pulmonary artery rings, canine coronary arteries, bovine coronary arteries, and the rat caudal artery. They have also been implicated in mediating bradykinin induced vasodilation in rat heart and kidney. It has been suggested that the vasodilator actions of EETs may be endothelial dependent due to modification by cyclooxygenase.

Cytoxygenase dependent vasoactivity of 5,6-EET has been shown to have two components: release of vasodilator prostanoids, PGE2 and PGI2, and metabolism of 5,6-EET to a prosta glandin analog 5,6-epoxy-PGE2. It has been suggested that the mechanism of vasodilatation of the EET may be by opening endogenous K+ channels, and regional variability of EET action may be related to further modification by local endothelial factors. On the other hand, 20-HETE has been shown to be a potent vasoconstrictor of isolated rat aorta, rabbit mesenteric carotid and renal arteries, dog renal microvessels, and cat cerebral microvessels. The vasoconstrictor activity of 20-HETE has also been suggested to be endothelial and cyclooxygenase dependent. Studies by Pfister et al suggest that hypercholesterolemia may alter arachidonic acid metabolism in rabbit aorta. The significance of these findings needs to be confirmed in future studies.

**Renal Actions** The cytochrome P450-dependent metabolites of arachidonic acid have been shown to influence several aspects of renal function (Table 1).

**Renal Microcirculation** EETs have been shown to be mitogenic, to stimulate [3H]-thymidine incorporation, and to activate Na+/H+ exchange in cultured rat glomerular mesangial cells. This suggests a role for these metabolites in cell proliferation and mesangial expansion accompanying diabetic nephropathy and other forms of glomerular pathology. Studies of the effects of these products on renal microcirculation have produced conflicting results in rabbit compared with rat kidney. In isolated perfused rabbit kidney, 5,6-, 8,9-, and 11,12-EET had a vasorelaxant action, whereas in
TABLE 1. SUMMARY OF BIOLOGICAL ACTIONS OF CYTOCHROME P450-DEPENDENT METABOLITES OF ARACHIDONIC ACID

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Activity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EET</td>
<td>Vasodilator in many vascular beds</td>
<td>7, 43, 49</td>
</tr>
<tr>
<td></td>
<td>Vasoconstrictor in rat renal artery</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Relax guinea pig hilar bronchi</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Mitogenic in glomerular cells</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Inhibit platelet aggregation</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Stimulate release of luteinizing hormone, somatostatin, prolactin</td>
<td>47, 48, 71</td>
</tr>
<tr>
<td></td>
<td>Stimulate release of glucagon</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Induces Ca(^{2+}) influx into cells, inhibit Ca(^{2+}) entry into platelets</td>
<td>72, 73</td>
</tr>
<tr>
<td></td>
<td>Increases cell shortening and calcium concentration in ischemic myocardial cells</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Alters Na(^+)/K(^-) flux and transepithelial voltage</td>
<td>75</td>
</tr>
<tr>
<td>DHET</td>
<td>Inhibit hydroosmotic effect of AVP</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Inhibit osmotic flow in toad bladder</td>
<td>76</td>
</tr>
<tr>
<td>12-HETE</td>
<td>Inhibits Na(^+),K(^-)-ATPase</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Inhibits renin secretion from rat renal cortex</td>
<td>78</td>
</tr>
<tr>
<td>19-HETE</td>
<td>Stimulates Na(^+),K(^-)-ATPase</td>
<td>79</td>
</tr>
<tr>
<td>20-HETE</td>
<td>Vasoconstrictor</td>
<td>7, 43, 49</td>
</tr>
<tr>
<td></td>
<td>Contracts guinea pig hilar bronchi</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Inhibits Na(^+),K(^-)-ATPase</td>
<td>80</td>
</tr>
<tr>
<td>20-COOH-AA</td>
<td>Inhibits Na(^+),K(^-)-ATPase, (^{86})Rb uptake</td>
<td>80, 20</td>
</tr>
</tbody>
</table>

rat kidney 8(S)9(R)-EET elicited dose-dependent vasoconstriction and reduction in GFR.\(^6\) This may again reflect the importance of local endothelial factors as modifiers of the action of these eicosanoids.

Imig et al\(^4\) showed that inhibitors of cytochrome P450 attenuate the vasoconstrictor response of afferent arterioles to elevation in renal perfusion pressure and impair autoregulation of glomerular capillary pressure. Zou et al\(^6\) confirmed this and implicated 20-HETE as a modulator of autoregulation of renal blood flow. Takahishi et al\(^6\) demonstrated that following uninephrectomy in rats, the cytochrome P450 linked arachidonate enzymatic activity was specifically induced in the remaining kidney. They postulate that production of vasoconstrictor metabolites by stimulation of this pathway may act as a counter regulatory mechanism in mitigating the hyperperfusion and hyperfiltration that develop following uninephrectomy.

**Proximal Tubule** Studies have demonstrated that in the rabbit proximal tubule, angiotensin II stimulates 5,6-EET and possibly other epoxides in rabbit and rat.\(^1\) 5,6-EET can cause calcium influx through voltage sensitive channels\(^2\) and modify ion transport through Ca\(^{2+}\)-calmodulin dependent regulation of a variety of ion transporters that include the Na\(^+\)/H\(^+\) antiporter and/or the Na\(^+\),K\(^+\)-ATPase. Therefore, it has been hypothesized that angiotensin II induced natriuresis, and inhibition of renin secretion may be mediated by an arachidonic acid epoxygenase in the proximal tubule. Recent studies by Ribiero et al\(^1\) suggest that inhibition of Na\(^+\),K\(^+\)-ATPase activity in the proximal tubule by PTH may be mediated by activation of omega-hydroxy-

lase activity and production of 20-HETE. This action has been better characterized in mTALH cells as is detailed below. Zou et al have also suggested a role for 20-HETE in tubuloglomerular feedback.\(^4\)

**Medullary Thick Ascending Loop of Henle (mTALH)** The cells of the medullary thick ascending loop of Henle (mTALH) play a major role in regulation of extracellular fluid volume by their high capacity to absorb NaCl. These cells contain high concentrations of Na\(^+\),K\(^+\)-ATPase, which plays a key role in active translocation of sodium across the basal membrane coupled with hydrolysis of ATP. Schwartzman et al\(^2\) initially demonstrated that incubation of arachidonic acid with mTALH cells resulted in formation of products that were potent inhibitors of Na\(^+\),K\(^+\)-ATPase. Carroll et al\(^8\) confirmed these findings and identified 20-COOH-AA and 20-HETE as potent inhibitors of Na\(^+\),K\(^+\)-ATPase in mTALH cells. 12 (R)HETE, 5,6-EET, 11,12-EET, and 11,12-DHET have also been shown to be potent inhibitors of Na\(^+\),K\(^+\)-ATPase.\(^7\)\(^8\) 19(S)-HETE, however, is a potent stimulator on this pump.\(^7\) Inhibition of Na\(^+\),K\(^+\)-ATPase by oxygenated arachidonic acid metabolites has also been demonstrated by other authors.\(^8\)

Escalente et al\(^8\) studied the effects of cytochrome P450-dependent arachidonic acid metabolites on ion transport in mTALH cells by measuring \(^{86}\)Rb uptake and manipulating the flux of arachidonic acid through the P450 pathway.\(^8\) \(^{86}\)Rb movement reflects that of K\(^+\), and as K\(^+\) is cotransported with Na\(^+\) and Cl\(^-\) in mTALH, \(^{86}\)Rb movement is a reliable estimate of mTALH transport function. They demonstrated that
arachidonic acid inhibits $^{86}$Rb uptake in mTALH cells and, by using inhibitors, showed that this effect is mediated by products of the P450 pathway (likely 20-HETE and 20-COOH-AA). Staudinger et al. studied this further and identified 14,15-EET as a potent inhibitor of $^{86}$Rb uptake, likely via an amiloride sensitive mechanism.

Further evidence for a role in sodium balance was provided when Capdevila et al. demonstrated that dietary salt loading of rats resulted in significant increases in EET and DHET levels in the urine. When a cytochrome P450 inhibitor, clotrimazole, was added, there was a significant decrease in epoxygenase metabolite excretion and increase in blood pressure. This suggests that these metabolites may play a functional role in the kidney response to excess salt. The mechanism may involve inhibition of sodium reabsorption in the proximal and distal nephron by modulation of Na$^+$/K$^+$/Cl$^-$ or Na$^+$/K$^+$-ATPase activity. This would represent an adaptive response to increased dietary salt preventing salt retention. The extent to which these metabolites mediate salt sensitivity of blood pressure regulation in humans has not been determined. In the rabbit cortical collecting duct, the DHETs, particularly 14,15-eicosanoid metabolites of arachidonic acid metabolism. In a similar set of experiments, hemodialysis resulted in corresponding reductions in blood pressure, whereas no difference was present in 20-week-old rats. This increase of arachidonic acid conversion to the cytochrome P450-dependent metabolites was coincident with the greatest increase in blood pressure, and once the blood pressure was established by 20 weeks of age, there were no differences between SHR and WKY in cytochrome P450-dependent metabolism of arachidonic acid.

Further support for this hypothesis was provided by Omata et al. These authors demonstrated an age related increase in the production of all renal cytochrome P450 arachidonic acid metabolites in SHR and the most significant increase was in the production of 20-HETE (a potent vasoconstrictor) between 3 and 13 weeks of age. The same pattern of rise was noted in the WKY rats but the magnitude of increase was significantly lower. 20-HETE can undergo further oxidation to 20-COOH-arachidonic acid, and the production of this metabolite was 2 to 8 times higher in the SHR from fetus to 7 weeks of age, indicating a higher rate of oxidation of 20-HETE. These temporal relationships are consistent with involvement of the renal cytochrome P450-dependent metabolites in the progressive elevation of blood pressure in the developmental stages. The potent vasoconstrictor action and sodium retention of these products may potentiate development of hypertension in the young SHR.

Further credence was lent to this hypothesis when it was demonstrated that treatment of 7-week-old SHRs with stannous chloride (SnCl$_2$) reduced blood pressure, whereas it was without effect in the 20-week-old rats. Stannous chloride is known to induce heme oxygenase and cause depletion of renal cytochrome P450. It was shown in this study that there was a significant reduction in the production of cytochrome P450-dependent arachidonic acid metabolites when treated with stannous chloride. In fact, a dose-response relationship could be demonstrated in the young SHR. Thus, increasing doses of stannous chloride resulted in corresponding reductions in blood pressure and in renal cortical microsomal arachidonic acid metabolism. In a similar set of experiments, heme arginate, another inducer of heme oxygenase, selectively prevented the elevation of blood pressure in the young SHR and reduced formation of 19- and 20-HETEs. However, stannous chloride induction of heme oxygenase also results in production of carbon monoxide, which is a vasodilator, thus confounding interpretation of these results. We also speculate that stannous chloride may have the potential to influence nitric oxide synthase activity and produce vasodilating factors via the cyclic GMP pathway.

In the SHR, papillary blood flow is reduced requiring an elevated mean perfusion pressure to normalize papillary blood flow and hydrostatic pressure to maintain sodium balance. It has been suggested that this decline in papillary blood flow may be due to enhanced vascular tone rather than structural changes.
in the deep nephrons. Imig et al. confirmed that the vascular tone in the preglomerular vasculature of the young SHR was elevated, and that inhibitors of cytochrome P450 produced vasodilatation of the afferent arteriole and attenuated their pressure-dependent vasoconstriction. The production of 20-HETE was also shown to be significantly elevated in the SHR. Since 20-HETE has been shown to be a potent vasoconstrictor, its elevation in this setting of elevated vascular tone suggests a potential role for this product in the regulatory responses of the afferent arteriole and resetting of the pressure natriuresis equation seen in this animal model. All the above observations in the SHR are consistent with a critical role of this family of eicosanoids in the development and maintenance of hypertension in this animal model.

Ma et al. studied the formation of cytochrome P450-dependent metabolites of arachidonic acid in the prehypertensive Dahl salt sensitive rats. They found that in cortical microsomes the production of 20-HETE was similar in salt-sensitive and salt-resistant rats, however the production of epoxygenase metabolites was less in the salt-sensitive rats. In the medullary microsomes, the 20-HETE production was lower in the salt-sensitive rats. This suggests that renal metabolism of arachidonic acid through the cytochrome P450-dependent pathway is altered in the prehypertensive Dahl salt-sensitive/Jr rats. However, the functional significance of these alterations needs to be established in this model.

Carroll et al. demonstrated that in rabbits in which coarctation of the aorta was induced, the production of cytochrome P450 metabolites by the mTALH cells was doubled by the eighth day following surgery, as compared with sham-operated rabbits. They hypothesized that these metabolites may exert a defensive function to limit the degree of mTALH cell injury in response to renal hypoperfusion associated zonal anoxia by reducing energy dependent Na⁺,K⁺-ATPase activity and affecting local vasodilatation.

**EVIDENCE IN HUMANS**

Given the impressive body of evidence from isolated nephron segments, cells in culture, and animal models, attempts are being made to correlate the cytochrome P450-dependent metabolites of arachidonic acid to human hypertension. EET have been documented to be endogenous constituents of human urine and kidney. Kidney biopsies from patients with hypernephroma were shown to have significant amount of EET as compared with control tissue. Moreover, variation in the amount of cytochrome P450 products up to 100-fold suggests the possibility of genetic polymorphism.

In a pilot study of 17 subjects, Jacobson et al. demonstrated that the urinary excretion of EETs was significantly higher in the hypertensive compared with the normal subjects. The patients with poorly controlled blood pressures had higher levels of EET excretion.

Furthermore Catella et al. demonstrated that urinary excretion of 11,12- and 8,9-DHETs were increased in healthy pregnant women compared to non-pregnant women, whereas 11,12- and 14,15-regioisomers were specifically increased in patients with pregnancy-induced hypertension. Further studies need to be done in humans to explore the role of this family of eicosanoids in human hypertension and renal pathophysiology.

**SUMMARY**

Arachidonic acid metabolism through the cytochrome P450-dependent pathway has been a subject of considerable interest during the last few years, and the influence of its metabolites on a variety of aspects of cardiovascular and renal function has been delineated. Of particular interest is the inhibition of Na⁺,K⁺-ATPase demonstrated by Schwartzman et al. An endogenous modulator of Na⁺,K⁺-ATPase activity has long been sought, having been postulated to account for rapid adjustments in sodium reabsorption and potassium excretion by the nephron. The cytochrome P450 pathway may serve as a common mechanism that mediates changes in sodium and chloride excretion in response to hormones and to changes in renal perfusion pressure, as well as to natriuretic substances including circulating inhibitors of Na⁺,K⁺-ATPase activity, which may be elevated in hypertension. Thus, alteration in the production of these metabolites may result in sodium retention and systemic hypertension and represent a compensating factor to maintain sodium balance.

Another facet of arachidonic acid metabolism by the cytochrome P450 system is that these metabolites can be further transformed by cyclooxygenase and acquire different biological activities. McGiff et al. have hypothesized that this ability to affect transport within the tubular segment of their origin, and then undergo transformation by adjacent tissues, may serve as a mechanism coupling changes in transport function of a tubular segment to changes in renal blood flow.

Research into the cytochrome P450-dependent metabolism of arachidonic acid has come a long way since being regarded as a “biochemical quirk.” Further studies are needed to explore the role of these metabolites in various aspects of human hypertension, including salt sensitivity and racial/ethnic differences in pathophysiology and prevalence.
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