Epoxide hydrolase and epoxygenase metabolites as therapeutic targets for renal diseases

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epoxyeicosatrienoic acids; endothelium-derived hyperpolarizing factor; hypertension; nephropathy; inflammation

A MAJOR CAUSE OF MORBIDITY and mortality is the progression of organ damage associated with renal and cardiovascular diseases. For instance, the incidence of end-stage renal disease (ESRD) is escalating and the number of patients on dialysis is predicted to double over the 10-yr period of 2000–2010 (7, 9, 19, 34, 104). The two main diseases responsible for the increase in ESRD are diabetes and hypertension. One contributing factor to end-organ damage is an impaired endothelium (6, 21, 56, 60, 95). Interestingly, endothelial dysfunction has recently been touted as a marker for unfavorable cardiovascular prognosis in humans (5, 27, 66). Others and we have established that cytochrome P-450 (CYP) metabolites (CYP2C) produced by the endothelium have antihypertensive properties and proposed that the epoxyeicosatrienoic acids (EETs) are endothelium-derived hyperpolarizing factors (EDHFs) (2, 12, 30, 43, 50, 87). Additionally, EETs have profibrinolytic effects, anti-inflammatory actions, and inhibit smooth vascular muscle cell migration (11, 20, 32, 78, 79, 94). Recent interest has also focused on the role of soluble epoxide hydrolase (SEH) in renal and cardiovascular disease and inhibition of this enzyme as an avenue to increase EET levels. This review will highlight these favorable EET properties that could protect the kidney from ESRD during renal and cardiovascular disease states.

EPOXYGENASE METABOLITES AS AN EDHF AND BEYOND

The contribution of the endothelial cells to the control of blood flow has been recognized for over two decades. Earlier studies established that endothelium-derived factors could act on vascular smooth muscle cells to relax or contract arteries (38, 68). The identity of nitric oxide and prostaglandins as the main products of the endothelial cells that relax the vascular smooth muscle has been well established (10, 38, 67, 68). In addition, the fact that the endothelium released one or more substances that relaxed vascular smooth muscle cells through membrane hyperpolarization was also repeatedly demonstrated (10, 67, 95). A number of studies have provided evidence that this nitric oxide- and cyclooxygenase (COX)-independent endothelium-derived relaxing factor was a metabolite of the arachidonic acid cascade (10, 36, 67, 95). It was also postulated that the unidentified EDHF hyperpolarized vascular smooth muscle cells by activating calcium-activated K+ channels (KCa) (43, 50, 95). Nevertheless, the identity of this EDHF remains elusive and the exact identity of the one or more EDHFs continues to be debated.

There is strong and convincing evidence that epoxygenase metabolites are renal vascular EDHFs. EET vascular responses

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have been difficult to assess in the past because COX, SEH, and other enzymes can metabolize epoxygenase metabolites. Although renal vascular resistance can either increase or decrease in response to infused regioisomeric EETs, the increase in renal vascular resistance is COX dependent in most of these cases (17, 36, 43, 50). In contrast, the direct application of EETs to renal smooth muscle cells consistently results in dilation and activation of $K_{Ca}$ channels (50, 112). This direct application of EETs to the renal microvasculature permits investigation of the vascular smooth muscle cell actions of these metabolites and avoids possible metabolism or degradation that would occur during infusion to an isolated vascular bed. Adventitial administration of 11,12-EET and 14,15-EET dilates the afferent arteriole and this vasodilation is independent of COX activity (50). The corresponding diols, dihydroxyeicosatrienoic acids (DHETEs), lack renal vascular dilator activity (50, 112). DHETEs are generated from EETs by the action of SEH and in a number of vascular systems the diols either have decreased actions or are devoid of activity (43, 87, 105). 5,6-EET is another EDHF candidate because 5,6-EET decreases renal perfusion pressure in the Wistar-Kyoto and spontaneously hypertensive (SHR) rats (80). Interestingly, 11,12-EET and 14,15-EET are the two epoxides of arachidonic acid that most consistently demonstrate vascular smooth muscle cell-relaxing properties and other cardiovascular protective activities (12, 43, 78, 87, 105). Although various regioisomeric EETs are excellent candidates for being an EDHF in the kidney, the afferent arteriolar cellular signaling mechanisms of 11,12-EET are better understood.

The signaling mechanisms utilized by 11,12-EET to elicit dilation of the afferent arteriole clearly establish this epoxide as an EDHF in the kidney. 11,12-EET acts on pregglomerular vascular smooth muscle cells to dilate the arteriole (49, 50, 112). In addition, this epoxide activates renal microvascular smooth muscle cell $K_{Ca}$ channels (112). The ability of EETs to activate $K_{Ca}$ channels is not limited to the renal vasculature or vascular smooth muscle cells (2, 4, 12, 39, 59, 107). 11,12-EET and 14,15-EET have been demonstrated to activate $K_{Ca}$ channels in cerebral and coronary vascular smooth muscle cells (4, 12, 39, 59, 107). ADP ribosylation is one intracellular mechanism that has been demonstrated to activate $K_{Ca}$ channels in coronary arteries (59). More recently, epoxides have also been shown to hyperpolarize platelets by activating $K_{Ca}$ channels and 11,12-EET was the most potent of the regiosomer (58). Renal microvascular activation of $K_{Ca}$ channels appears to be mediated by cAMP stimulation of protein kinase A because an arteriolar dilation to the sultanonamide analog of 11,12-EET was substantially reduced by protein kinase A inhibition (49). Similarly, 11,12-EET induction of cultured rat aortic smooth muscle cell tissue-type plasminogen activator (t-PA) gene transcription requires activation of Gas, adenyl cyclase, and protein kinase A (79, 94). Taken together, the $K_{Ca}$ channel- and protein kinase A-mediated dilator actions of 11,12-EET on afferent arterioles are consistent with the concept that 11,12-EET is an EDHF (Fig. 1).

Further evidence for an epoxygenase metabolite as a renal EDHF has been attained from evaluation of vascular responses to bradykinin and acetylcarnone. Bradykinin and acetylcarnone are agents that elicit dilation by releasing nitric oxide, prostaglandins, and EDHF (10, 38, 67, 68). Isolated, perfused rat kidney studies were the first to provide evidence that a CYP metabolite contributes to the bradykinin-induced decrease in renal perfusion pressure (37). The development of specific epoxygenase enzyme inhibitors and EET antagonists has enabled investigators to selectively determine the contribution of epoxygenase metabolites to endothelium-dependent vasodilation. Epoxygenase inhibitors can significantly attenuate bradykinin-induced dilation of the afferent arteriole (48). The nitric oxide- and COX-independent rat afferent arteriolar dilation to bradykinin was eliminated by the epoxygenase inhibitor N-methylsulfonyl-6-(2-propargyloxyphenyl) hexamide (MS-PPOH) (48). As further support for involvement of EETs in the pregglomerular dilatory response to bradykinin, we demonstrated that renal microvascular EET levels were increased by bradykinin (48). A role for epoxygenase metabolites has also been reported for the afferent arteriolar response in the in vitro perfused hydropnephrotic rat kidney. Wang et al. (98) demonstrated that there were two components to the bradykinin EDHF response of the afferent arteriole. Besides the epoxygenase component, the combination of the $K^{+}$ channel inhibitors charybdotoxin and apamin blocked another bradykinin-mediated EDHF component that was CYP independent (98). The findings of this study and other studies suggest that endothelial cell charybdotoxin- and apamin-sensitive $K^{+}$ channels are activated and the resultant hyperpolarization may be transmitted to the underlying smooth muscle layer via myoendothelial gap junctions (88, 98). Last, there is also evidence that glo- merular EET production mediates bradykinin dilation of rabbit postglomerular efferent arterioles (86). Although multiple EDHFs appear to contribute to the renal microvascular dilator response to bradykinin, epoxygenase metabolites have been clearly established as an EDHF.

The possible contribution of epoxygenase metabolites to the acetylcarnone-mediated afferent arteriolar EDHF response remains unresolved. As has been observed in a number of
vasculatures, the EDHF portion of the afferent arteriolar dilation to acetylcholine is inhibited by the combination of charybdotoxin and apamin (97, 98). This acetylcholine EDHF dilatatory component was unaltered by the K<sub>a</sub> inhibitor tetraethylammonium or the CYP inhibitor 17-octadecenoic acid (97, 98). These studies have led to the postulate that acetylcholine activates endothelial K<sup>+</sup> channels to mediate EDHF vascular smooth muscle cell relaxation independently of CYP450 metabolites. On the other hand, acetylcholine-induced rabbit afferent arteriolar EDHF dilation can be inhibited by the EET metabolites. On the other hand, acetylcholine-induced rabbit afferent arteriolar dilator response to acetylcholine (96). Thus the exact contribution of EETs to acetylcholine-induced EDHF responses is unresolved and necessitates additional experiments.

In addition to their contribution to endothelium-dependent vasodilators, EETs can also modulate responses to vasoconstrictors. Afferent arteriolar responses to angiotensin are enhanced by CYP inhibition (45). Additionally, rabbit afferent arteriolar dilation to angiotensin has been attributed to angiotensin type 2 (AT<sub>2</sub>) receptor activation and EET generation (3). Afferent arteriolar constrictor responses to endothelin-1 (ET-1) are also opposed by epoxygenase metabolites (51). The ability of EETs to counteract the ET-1 constriction of the afferent arteriole did not involve regulation of calcium at the level of the vascular smooth muscle cell because MS-PPOH did not alter the calcium response (51). Similarly, selective epoxygenase inhibitors have also been demonstrated to enhance the afferent arteriolar constriction to elevations in renal perfusion pressure (46). These findings are consistent with the concept that epoxygenase metabolites act as dilators and are a vital component of renal hemodynamic responses.

Another aspect related to EETs biological actions that are garnering attention and excitement are their anti-inflammatory, proliferative, antiinflammatory, and antithrombotic properties. A connection between inflammatory cytokines and CYP2C enzymes has been clearly established. In regard to the CYP2C enzymes, interleukin-1 (IL-1) suppresses CYP2C11 gene expression in rat hepatocytes via NF-κB binding at the transcription start site (42). IL-6 has also been shown to downregulate CYP2C11 mRNA (73). Intriguingly, cytokines result in the downregulation of endothelial cell CYP2C enzymes and reduce EET-mediated relaxation (54). Node et al. (78, 79) provided the initial evidence that EETs possess antiinflammatory properties. These investigators demonstrated that 11,12-EET inhibited TNF-α-elicited expression of VCAM-1 and activation of NF-κB (26, 78, 79). Overexpression of the epoxygenase CYP2J2 enzyme in endothelial cells also inhibited NF-κB promoter activity (78). EETs have also been demonstrated to inhibit the aggregation of human polymorphonuclear leukocytes (31, 41, 83). Additional support for EETs as anti-inflammatory is provided by the fact that 11,12-EET attenuates, whereas CYP inhibitors induce, the pyretic response to IL-1β and the febrile response to lipopolysaccharide injection (57, 77). These initial findings provide initial evidence that EETs possess anti-inflammatory properties in addition to their vasodilatory actions.

The discovery of CYP2C enzymes as a source of reactive oxygen species in blood vessels appears to be a downside for renal and cardiovascular protection (29, 33). Induction of CYP2C enzymes enhances NF-κB activity and VCAM-1 expression; however, 11,12-EET was demonstrated to attenuate NF-κB activity in cultured endothelial cells (33). Additionally, the CYP inhibitor sulfinpyrazone has recently been shown to enhance endothelium-dependent responses in patients with coronary artery disease (28). CYP inhibition also attenuated the TNF-α-induced increase in cultured endothelial cell monosialic acid expression (89). Interestingly, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors have been demonstrated to induce CYP2Cs, enhance EDHF arterial relaxation, but generate reactive oxygen species (29). Epoxygenase enzyme overexpression has also been shown to protect blood vessels from hypoxia-reoxygenation injury (100). Overall, these studies suggest that CYP2C generation of reactive oxygen species in some instances may be counteracting the beneficial actions of EETs.

The proliferative and antiinflammatory actions of EETs suggest that EETs are very important for maintaining renal and vascular homeostasis. Growth-mediated actions of EETs are complex and highly suggestive that EETs contribute importantly to vascular injury processes. One consistent finding is that EETs promote endothelial cell proliferation (64, 76, 81, 82). This has been best demonstrated in human endothelial cells that overexpress CYP2C (64, 81, 82). Endothelial proliferation induced by CYP2C9 overexpression or incubation with 11,12-EET activates MAP kinase and upregulates cyclin D1 (82). The endothelial cell response to 11,12-EET also involves phosphatidylinositol 3-kinase (PI3-K) activation of Akt and subsequent inactivation of forkhead box, class O family of transcription factors (81). Interestingly, 14,15-EET activates PI3-K and MAP kinase in renal epithelial cells and promotes proliferation (8, 15, 16). Activation of Src kinase and utilization of the EGF receptor as a scaffold and the resulting MAP kinase activation also appear to be required for 14,15-EET endothelial cell proliferative responses (14-16). In contrast, the vascular smooth muscle cell responses to EETs have been antimigratory (94). 11,12-EET and CYP2J2 overexpression inhibited rat aorta smooth muscle cell migration in response to serum-derived growth factor or PDGF (94). One confounding finding is that SEH inhibitors attenuate human aortic vascular smooth muscle cell proliferation that is suggestive of an antiproliferative EET action (20). Taken as a whole, these studies imply that EETs are vital components of the renal and vascular response to injury; however, the exact function of epoxygenase metabolites in renal and vascular growth-mediated responses remains to be determined.

Another intriguing action of EETs that would be renal and cardiovascular protective is their profibrolytic activity. Interestingly, the first evidence that EETs possessed antithrombotic actions predates the first description of EET vasodilatory actions (31, 84). All four EET regioisomers were demonstrated to inhibit arachidonic acid-induced aggregation of human platelets (31, 63). More recently, EETs have been demonstrated to induce t-PA expression and hyperpolarize platelets (58, 79). The hyperpolarization of platelets by EETs was associated with an inhibition of their adhesion to cultured endothelial cells (58). As with many other renal and vascular actions attributed to epoxygenase metabolites, 11,12-EET was the most active metabolite (58, 79). Thus EETs may protect the kidney from cardiovascular disease by enhancing fibrinolytic activity and inhibiting platelet adhesion.
Overall, epoxygenase metabolites are an EDHF and are involved in the renal vascular responses to hormones associated with renal and cardiovascular diseases. Moreover, the EET vascular actions beyond those of an EDHF are intriguing. These findings have led investigators to determine the regulation of epoxygenase metabolites during renal and cardiovascular diseases. The possible contribution of the SEH enzyme to the regulation of EET levels and blood pressure regulation is another intriguing area of investigation. Consequently, the renal and cardiovascular protective actions of EETs and SEH are vigorously being explored.

**RENAIJI AND CARDIOVASCULAR PROTECTIVE ACTIONS OF EETs AND SEH**

It has been recognized for a number of years that CYP metabolites and more specifically renal EETs are involved in renal blood flow regulation and long-term arterial blood pressure control (13, 50, 62, 70, 87). In addition, reports have suggested a significant role for CYP2C and SEH enzymes in the long-term regulation of endothelial function and arterial blood pressure (35, 52, 70, 93, 103). As for the clinical practice, endothelial dysfunction is used as a diagnostic tool and can be a primary target for determining the efficacy of cardiovascular therapy (5, 6, 27, 66). Intriguingly, the protective effects that promote a healthy endothelium coincide with many of the recently described actions of EETs (Fig. 2) (2, 11, 12, 20, 30, 50, 78, 79, 94). Past investigations and recent developments in the areas of CYP2C, epoxygenase metabolites, and epoxide hydrolase that led to their identification as potential renal cardiovascular therapeutic targets will be reviewed.

The regulation and biological actions of epoxygenase metabolites have led to extensive study of these metabolites in blood pressure regulation. As mentioned previously, epoxygenase metabolites can be potentially vasococontractor actions of the prohypertensive hormones ET-1 and angiotensin (43, 45, 51). In addition to their vascular actions, epoxygenase metabolites affect the flux of ions across epithelial cell membranes, affect cell proliferation, and stimulate hormonal release (13, 40, 43). Regulation of renal EET production has also been intensively studied because the kidney has a relatively high epoxygenase activity (13, 87, 105). CYP2C enzymes and epoxygenase metabolites increase in response to a high-salt diet, and the CYP2C23 appears to be the major epoxygenase in the rat kidney (13, 62, 109). The contribution of CYP metabolites to the pressure-natriuretic response and translocation of tubule sodium transporters has also been established; however, the exact contribution of EETs and the hydroxylase product 20-HETE remains to be determined (22, 44, 106, 108). An increase in EET levels in response to a diet high in sodium would be expected to cause natriuresis because epoxygenase metabolites act to increase renal blood flow and decrease sodium reabsorption (13, 43, 70). As a consequence, hypertension develops in rats that have been administered an epoxygenase inhibitor and fed a high-salt diet (62). Thus regulation of CYP2C enzymes and EETs is important for maintaining body fluid and electrolyte homeostasis and blood pressure in response to a high-salt diet.

Intriguingly, one main finding has been that an inability to increase renal EET levels in response to a high-salt diet has been associated with the elevation in blood pressure observed in salt-sensitive hypertension (62, 65, 69, 109). The elevation in blood pressure and development of hypertension in the Dahl salt-sensitive rats fed a high-salt diet is associated with an inability of these animals to increase renal EET production (61, 62, 87). Lyon hypertensive rats also have a decreased renal epoxygenase activity that contributes to the increase in arterial blood pressure (65, 69). Transgenic rats overexpressing both human renin and angiotensinogen genes (dtGR) develop hypertension and renal failure that are associated with decreased kidney epoxygenase enzymatic activity and CYP2C11, CYP2C23, and CYP2J protein levels (53, 74, 75). Similarly, we have found that an inability to increase renal cortical and vascular CYP2C11 and CYP2C23 protein expression may contribute to salt sensitivity of angiotensin-dependent hypertension (109, 110). Although the CYP2J epoxygenase enzymes are present in the kidney, CYP2J expression does not change in response to a high-salt diet (109). Renal vascular expression of the CYP2J enzyme is decreased in angiotensin-infused rats fed a high-salt diet and could contribute to vascular dysfunction in this type of hypertension (109). Taken together, these studies suggest that increasing epoxide levels in angiotensin-dependent hypertension could lower blood pressure and protect the kidney (Fig. 3).

Even with the promise of epoxygenase metabolites to protect the kidney and vasculature, it has been difficult to assess the possible therapeutic actions of EETs chronically in vivo. Overexpression of epoxygenase enzymes has been used successfully in cell cultures and has only recently been translated to animals (33, 82, 91, 100). Two other approaches have been taken to chronically increase EET levels and determine the epoxide’s renal and vascular beneficial actions. One approach has been to induce renal CYP enzymes with peroxisome proliferator-activated receptor-α (PPARα) activators. PPARα activators, such as fenofibrate and clofibrate, induce CYP2C and CYP4A enzymes and lower triglyceride levels. The second approach has been to inhibit the conversion of the epoxides to their corresponding diols by SEH. As mentioned earlier, SEH

![Fig. 2. Renal and cardiovascular protective actions attributed to EETs and soluble epoxide hydrolase (SEH) inhibition. Arachidonic acid can be metabolized to EETs primarily by CYP2C enzymes. EETs are metabolized to biologically less active or inactive dihydroxyeicosatrienoic acids (DHETEs) by SEH (left). The table on the right represents known vascular actions of EETs or SEH inhibitors and the corresponding references.](image-url)
Muller et al. (75) recently demonstrated that PPAR damage associated with angiotensin hypertension (52, 111). Up to 10 days lowered blood pressure and ameliorated renal (103). Similarly, SEH inhibitors administered chronically for a period was observed after a single dose of an SEH inhibitor investigated. Blood pressure lowering in SHR over a 24-h period is responsible for the hydrolysis of EETs to the less active DHETEs. Fortunately, this enzyme represents a single known and highly conserved gene product with over 90% homology among humans, rats, and mice and can be selectively inhibited by a variety of urea, carbamate, and amide derivatives (52, 55, 71, 72, 93, 103). Each of these approaches has advantages and limitations; however, recent studies that have used these tactics in animals clearly demonstrate that epoxygenase metabolites protect the kidney from hypertension-induced damage (75, 111).

Evidence is mounting that increasing epoxide levels do have cardiovascular and renal protective actions. In this regard, acute elevations in EET levels or chronic induction of epoxygenase enzymes improve renal vascular responses, lower blood pressure, and decrease renal damage in angiotensin-dependent hypertension (47, 52, 111). Angiotensin-dependent models and human essential hypertension are associated with an enhanced vascular reactivity that is selective for angiotensin (1, 18, 27, 71, 72, 93, 103). Each of these approaches has advantages and limitations; however, recent studies that have used these tactics in animals clearly demonstrate that epoxygenase metabolites protect the kidney from hypertension-induced damage (75, 111).

The decreased EET levels contribute to increased endothelial dysfunction, blood pressure, and glomerular injury. Inhibiting the SEH enzyme (inset) is one approach to increase EET levels and oppose the renal and vascular damage that occur during renal and cardiovascular diseases.

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The overall potential of epoxides and epoxide hydrolase inhibition to provide beneficial renal and cardiovascular actions in disease states is beginning to be realized. Other studies have demonstrated that elevating 11,12-EET levels or CYP2J overexpression provides blood vessels and the heart protection from hypoxia-reoxygenation injury (23, 91, 100). Addition of 11,12-EET to transplant preservation solutions can help maintain endothelial function in coronary arteries (101). Although the future of epoxygenase metabolites as therapeutic targets looks bright, a number of areas still need to be addressed. A couple of things that have remained elusive since the first biological actions of EETs were described: whether receptors for epoxygenase metabolites exist and how intracellular signaling events are triggered by EETs. In this regard, EET mimetics are already helping investigators to understand the structural activity requirements for biological activity (25, 26). Identification of a binding site or receptor for EETs will undoubtedly open up new avenues for investigation. Like epoxygenase metabolites, new developments with SEH inhibition are on the horizon. The recent findings concerning the epoxide hydrolase (EPHX2) gene in humans and localization to renal and vascular tissues suggest that experimental findings could be translated to patient care (24, 85, 102). Newly developed SEH inhibitors have better chemical properties that allow these compounds to be administered chronically and orally to rodents (55). Fatty acid binding proteins have the ability to increase epoxide levels or inhibit epoxide hydrase will be developed in the future and may possibly provide beneficial actions beyond the renal and cardiovascular actions described to date.

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