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Role of Cyp-epoxygenase in regulating renal membrane transport and hypertension

Jorge Capdevila¹ and Wenhui Wang²

¹Department of Medicine, Vanderbilt University, Nashville, TN

²Department of Pharmacology, New York Medical College, Valhalla, NY

Abstract

Purpose of review—CYP-epoxygenase metabolism of arachidonic acid (AA) plays important roles in regulating renal Na transport and afferent arterioles vasoactivity. In the past several years, progress has been made in characterizing the specific CYP-epoxygenases responsible for the regulation of renal Na transport and in exploring the mechanism by which they modulate tubular sodium(Na) transport, preglomerular arteriole blood flow, and blood pressures. This review summarizes and updates recent progress in this area of research.

Recent Finding—CYP-epoxygenase metabolites of AA inhibited epithelial Na channel (ENaC) in the cortical collecting duct (CCD) and 11,12-epoxyeicosatrienoic acid (11,12-EET) was mainly responsible for mediating the inhibitory effect on ENaC. Down-regulation of CYP2C44 abolished AA-mediated inhibition of ENaC and increased ENaC activity. Additionally, 11,12-EET stimulated Ca²⁺- activated big-conductance K channels (BK) in the CCD and afferent arterioles smooth muscles. Furthermore, in preglomerular arterioles, inhibition of PP2A attenuated the stimulatory effect of 11,12- EET on BK.

Summary—CYP-epoxygenase-mediated suppression of renal Na transport is partially achieved by inhibition of ENaC activity in the CCD by CYP2C44 derived EETs. Stimulation of PP2A contributes to the EET-mediated vasodilation and activation of BK channels in preglomerular arterioles.

Introduction

Cytochrome P450s (CYP) belong to a gene superfamily whose members share a conserved *cysteiny*l peptide that provides for heme ligation, and endows them with unique catalytic properties [1]. Based on amino acid sequence identity, P450s are organized in families (40 % identity) and subfamilies (55% identity), with approximately 57 genes identified in the human genome. In addition to their established roles in drug and xenobiotic metabolism [1], the "P450 arachidonic acid monooxygenase" branch of the AA metabolic cascade [2–5] catalyzes the NADPH-dependent oxidation of AA to: a) four regioisomeric epoxyeicosatrienoic acids (EETs) (5,6-, 8,9-, 11,12-, and 3 14,15-EET) [5] or "AA epoxygenase", and/or b) 19- and 20-hydroxyeicosatetraenoic acids (19- and 20-HETE) [5] or "AA ω / ω -1 hydroxylase" (Fig. 1). In most cells and organ tissues the EETs can be: a) hydrated to vic-dihydroxyeicosatrienoic acids (DHETs) by cytosolic epoxide hydrolase, b) degraded by β -oxidized, or acylated into cellular glycerophospholipids [2–5]. The

Corresponding Address: Dr. Wenhui Wang, Department of Pharmacology, New York Medical College, Valhalla, NY 10595, (tel) 914 594 4139, (fax) 914 347 4956, wenhui_wang@nymc.edu.

Disclosure

None

identification of EETs and 20-HETE as products of the in vivo metabolism of AA by rodent and human tissues [5], established the AA monooxygenase as formal metabolic pathway, and suggested a biological role for its metabolites. The complexity of the CYP enzyme system in which different CYPs metabolize AA to similar products, share extensive sequence homology and, in many cases, share immunological determinants [1,5] has complicated functional assignments to individual CYP-epoxygenase isoforms. Nevertheless, it is now widely accepted that members of the CYP2C subfamily, in particular rat CYP2C23 and mouse CYP2C44, are the predominant and functionally relevant kidney epoxygenases [4,5]. However, biological roles for the CYP2J epoxygenases are reported [6,7].

Previous studies demonstrating that: a) the kidney expression of CYP2C epoxygenases was dietary salt sensitive [8], and b) CYP2C-epoxygenase inhibition caused dietary salt sensitive hypertension [8], suggested roles for these enzymes in the in regulation of renal Na handling. Compelling evidence indicating a role for the CYP-epoxygenases in renal Na transport was obtained from studies with *Cyp4a10*($-/-$) mice [9]. Although CYP4A10 does not metabolize AA to EETs, disruption of the *Cyp4a10* gene down-regulated renal CYP2C44 expression, and *Cyp4a10*($-/-$) mice developed hypertension when fed high Na diets [9]. Importantly, amiloride normalized the blood pressures of salt loaded *Cyp4a10*($-/-$) mice, strongly suggesting a role for the CYP-epoxygenases in ENaC inhibition [9]. Additional role for the CYP2C-epoxygenases in modulating renal glomerular filtration was suggested by previous studies showing that EETs dilated preglomerular arterioles by stimulating vascular smooth muscle Ca^{2+} - activated BK channels [10]. Recent studies have provided new insights into the mechanisms by which the CYP-epoxygenase EETs regulate renal Na transport and activate BK channels in smooth muscle cells. The epoxygenases expressed in the rat kidney are CYP2C11, 2C23, 2C24 [8], while those in the mouse kidney include 2C29, 2C38, 2C39, 2C44 and 2J5 [11,12]. CYP2C23 and CYP2C44 have been identified as the major CYP2C epoxygenase in the rat and mouse kidney, and as one of the enzymes mainly responsible for 11,12-EET formation [8,9,12]. Recent studies with transgenic and/or gene knockout mice provided unique opportunities to characterize the role of specific CYP-epoxygenases in renal function. This review aims to summarize results from recent studies and to provide updated views of the potential physiological roles of these enzymes and their EET metabolites.

EET-inhibits ENaC in the CCD

Wei et al have used the patch-clamp technique in the isolated split-open CCD to examine the effect of EET on ENaC. Three lines of evidence indicated that CYP-epoxygenase metabolites of AA inhibited ENaC [13]: First, application of AA inhibited ENaC, an effect was blocked by MS-PPOH (an epoxygenase inhibitor) but not by COX or CYP ω -hydroxylase inhibitors. Second, the addition of 11,12-EET inhibited ENaC, the effect of 11,12-EET on ENaC was specific because 8,9-EET was inactive, and 14,15-EET had only modest effects on ENaC activity. Moreover, 11R,12S-EET, the major product of the CYP2C44-dependent AA metabolism was a selective and potent ENaC inhibitor [12,14]. Third, 11,12-EET was present in the CCD and its level was altered by Na diet [15]. The finding that EET inhibited ENaC was also confirmed in the cultured CCD cell lines (mpkCCD) [16]. Compelling evidence of a role for the CYP-epoxygenase in inhibiting ENaC was obtained from studies using CCDs from *Cyp4a10*($-/-$) mice [9], and showing that: a) while AA did not inhibit ENaC activity in these mice, the channel was inhibited by 11,12-EET, and b) the inhibition of ENaC with amiloride normalized the blood pressures of hypertensive, salt loaded, *Cyp4a10*($-/-$) mice [9]. More recently, we have observed that the inhibition of ENaC by adenosine is mediated by the activation of AA metabolism by CYP-epoxygenases. Because a high salt intake has been reported to increase adenosine level [17]

and kidney EET biosynthesis (19), adenosine may play a role in suppressing Na transport through activating CYP-epoxygenase in the CCD (Fig.2).

EET regulates K channels in the CCD

11,12-EET has been shown to inhibit the 18-pS inwardly-rectifying K channels, a main type of K channels in the basolateral membrane of CCD [18]. In contrast, 11,12-EET stimulates the Ca^{2+} -activated BK channel in the apical membrane of the CCD [18,19]. Blocking the basolateral K channel by 11,12-EET may be partially responsible for the 11,12-EET-mediated inhibition of Na transport in the CCD because suppression of basolateral K channels depolarizes the cell membrane potential thereby reducing the driving force for Na entry across the apical membrane (Fig.2).

The Stimulation of BK channels by 11,12-EET plays a role in mediating flow-stimulated and BK channel-dependent K secretion [19]. We have observed that inhibition of CYP-epoxygenase activity with MS-PPOH abolished the flow-stimulated and BK channel-dependent K secretion. It is well established that BK channels are involved in K secretion in response to a HK intake [20]. Stimulation of BK channels by 11,12-EET is expected to increase the apical K conductance thereby compensating the effect of decreased driving force for K secretion induced by 11,12-EET-mediated inhibition of ENaC. Therefore, 11,12-EET should play a role in stimulating renal K secretion during a HK intake which increased 11,12-EET formation [14].

11,12-EET dilates preglomerular arterioles and activates the BK channels by stimulating PP2A

Roles for the EETs in the adenosine $\text{A}_{2\text{A}}$ receptor mediated dilation of preglomerular microvessels were proposed based on the observation that inhibition of the CYP-epoxygenases abolished the adenosine effect [21]. Application of a metabolically more stable analog of 11,12-EET to afferent arterioles induced vasodilation, and the EET analog effects were blunted by inhibitors of the arteriole smooth muscle BK channel or serine/threonine protein phosphatase 2A (PP2A) [22]. Two additional lines of evidence suggested that the effects of 11,12-EET on Ca^{2+} -activated BK channels resulted from PP2A stimulation: 1) the 11,12-EET analog increases PP2A activity; and 2) the addition of PP2A activated BK channels in renal smooth muscles, an effect blocked by okadaic acid. However, the stimulation of the BK channel by 11,12-EET/PP2A may result from removal of a PKA-mediated channel inhibition. It has been shown that the alpha subunit of the BK channel has an splicing isoform containing a 59 amino acid insertion (STREX) [23], and that PKA inhibited the BK channels with STREX insertion (24). Since BK channels in the smooth muscle of afferent arterioles were inhibited by PKA-induced phosphorylation and activated by PP2A-mediated dephosphorylation, it is likely that they express STREX splice variants [24]. Hence, 11,12-EET activates the STREX variant of BK and causes afferent arteriole dilation by a PPA2 mediated pathway (Fig 3)

Regulation of EET biosynthesis

CYP2C23 and mouse CYP2C44 are the predominant AA epoxygenases in rat and mouse kidneys, respectively [8,9], they are up-regulated by high Na or K intake [9,25], and expressed in the CCD (26). Furthermore, under similar conditions, failed to increase a CYP2J2 immunoreactive protein which was also expressed in the CCD [26]. Moreover, doubling dietary K from 1% (control) to 2% stimulated, within 7 days, the expression of CYP2C23 and CYP2C44 in the rat and mouse kidney, respectively [14,27]. The up-regulation of these enzymes by a HK intake was unlikely to result from increases in aldosterone levels since low Na diets decreased kidney CYP2C23 expression (20) while

raising plasma aldosterone. In addition, angiotensin II and tumor necrosis factor α have been reported to decrease transcription and translation of several CYP epoxygenase including CYP2C44 in the kidney [28,29]. Inhibition of A_{2A} receptor in Dahl salt-resistant rats on a high salt diet decreased renal EET level and diminished urinary Na excretion thereby causing hypertension [21].

Lessons learn from knockout and transgenic mice

Transgenic mice provided physiologically-relevant information regarding the role of each specific epoxygenase. In the following section, we summarize the main findings obtained from epoxygenase knock-down or overexpression mice.

Cyp2c44(–/–) mice

In these animals, disruption of the *Cyp2c44* epoxygenase gene causes hypertension in the animals fed high K (2–10%) diets, while wild type mice on similar diets remain normotensive. The finding that AA failed to inhibit ENaC in the CCD of *Cyp2c44*(–/–) mice, while 11,12-EET was able to block the channel suggests that CYP2C44-derived EETs were responsible for suppressing ENaC activity during increasing dietary K intake, and preventing hypertension, as indicated by the scheme shown in Fig 4. High K intake is expected to increase aldosterone and thus stimulates Na-K-ATPase and ENaC expression in the aldosterone-sensitive nephron [30–32]. However, since a high K diet also stimulates CYP2C44 expression, the resulting increase in EET levels suppresses Na transport in the collecting duct. Lack of a functional CYP2C44 epoxygenase gene impairs the balance between aldosterone and EET thereby increasing Na absorption in the distal nephron. This view was supported by the metabolic cage studies showing that the *Cyp2c44*–/– mice have a diminished ability to excrete Na during increasing K intake, and by the fact that amiloride normalized the blood pressures of high K fed hypertensive *Cyp2c44* (–/–) mice (22).

Cyp2i5–/– mice

Disruption of the *Cyp2j5* gene had no effect on renal EET biosynthesis. However, female *Cyp2j5* (–/–) mice had low plasma levels of 17-beta-estradiol. Thus, female, but not male, *Cyp2j5*(–/–) mice are hypertensive and the mice have an enhanced hypertensive response to angiotensin II and endothelin-1[33]. Since estrogen replacement normalized the blood pressure and vascular responsiveness angiotensin II and endothelin, *Cyp2j5* may play a role in regulating sex hormone rather than EET biosynthesis.

Cyp4a10(–/–) and Cyp4a14(–/–) mice

Although *Cyp4a14*(–/–) and *Cyp4a10*(–/–) mice had the same hypertensive phenotype, the mechanisms causing hypertension were quite different [9,25]. In both mice models, the disrupted genes are not directly responsible for the hypertension but rather through a mechanism controlling the expression of surrogate pro- or anti-hypertensive P450 genes. *Cyp4a14*(–/–) mice showed male specific hypertension, linked to androgen-mediated increases in kidney CYP4A12 levels, pro-hypertensive 20-HETE biosynthesis, and renal vascular resistance [25]. In contrast, male and female *Cyp4a10*(–/–) mice showed dietary Salt sensitive hypertension, and while there was no difference between wild type and KO mice in kidney 20- HETE biosynthesis [9]. Hypertensive *Cyp4a10*(–/–) mice on high salt showed reductions in CYP2C44 epoxygenase expression, urinary EETs and DHETs, as well as small decreases in urine volume and Na concentration [9].

Mice with Endothelial overexpression of Cyp2j2 and Cyp2c8

Endothelium overexpression of human CYP2J2 or CYP2C8 epoxygenase suppressed the endothelin-1 induced vasoconstriction of afferent arterioles, and enhanced the vasodilation induced by acetylcholine [34]. Moreover, overexpression of CYP2J2 or CYP2C8 ameliorated the angiotensinII/high salt-induced glomerular injury (12).

Polymorphisms of Cyp epoxygenase

Human CYP2C8 and CYP2C9 are active AA epoxygenases [5], and CYP2J2 catalyzes AA epoxidation and ω -1 hydroxylation [35]. Animal studies pointed to the *CYP2C8*, *CYP2C9*, *CYP2J2*, and the *sEH* as candidate genes for studies of the molecular basis of human hypertension. The *CYP2C8* and *CYP2C9* are polymorphic genes [36,37], and four of their variants (*2C8*2*, *2C8*3*, *2C9*2* and *2C9*3*) catalyze AA epoxidation at markedly reduced rates [36–38]. Studies with Caucasian and African American cohorts failed to identify associations between any of these *CYP2C* variants and hypertension [36,37,39], however, lower CYP2C9*3 allele frequencies were reported in a subset of hypertensive Chinese women [40]. A *CYP2J2* promoter variant (G-50T) with reduced transcriptional activity has been associated with no effect, lower risk or higher risk of hypertension in studies using populations of different ethnicities [36,37,39]. Polymorphisms in the *sHE*, in coding and non-coding regions of the gene are described, and while associations between several of these variants and the risk of cardiovascular and/or coronary artery disease are reported [36,37], most studies have failed to document links between most of them and hypertension [36,37].

Conclusion

There is now convincing evidence of roles for the CYP AA epoxygenases in renal physiology and the regulation of distal Na transport and blood pressure in several animal models, as well as potential contributors to the pathophysiology of subsets of human hypertension. Among the many issues that remain outstanding in this area of research, we include: a) the characterization of the molecular mechanisms responsible for EET-mediated effects on membrane transport and ion channel activity; b) the study of signaling mechanisms for EETs, and the characterization of putative membrane bound receptors for these eicosanoids; c) the identification and molecular characterization of mechanisms that control the expression of CYP2C epoxygenases in a organ/tissue/cell specific fashion; and d) the analysis of correlations between human pathophysiological conditions and alterations in genes coding and/or responsible for their expression.

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Key Points

- > Cyp-epoxygenase metabolites inhibit ENaC.
- > Cyp2c44^{-/-} mice are hypertensive by increasing dietary K intake.
- > Cyp-epoxygenase metabolites dilate preglomerular arterioles by activating BK channels.
- > EET stimulates the BK channels by activating PP2A.

THE P450 ARACHIDONIC ACID MONOOXYGENASE

Fig. 1.

Reactions catalyzed by cytochrome P450 during arachidonic acid metabolism

Fig. 2.

A cell scheme illustrating the role of CYP2C44 in regulation of Na transport in the CCD. The inhibitory effect of 11,12-EET on ENaC is achieved by blocking apical ENaC and basolateral K channels. In addition, 11,12-EET mediates the adenosine-induced inhibition of ENaC.

BK channel alpha subunit **Fig. 3.**

A scheme illustrating the mechanism by which 11,12-EET activates the BK channels in smooth muscles of afferent arterioles. Asterisk represents 59 amino acid insertion (STREX) in the alpha subunit of the BK channels.

Fig. 4.

A scheme illustrating the role of CYP-epoxygenase-dependent AA metabolism in suppressing ENaC and in preventing excessive Na absorption in the CCD when dietary K intake increases. Solid line arrow and dotted line arrow represent a stimulation and an inhibition, respectively.