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Conflicting roles of 20-HETE in hypertension and renal end organ damage

Chao Zhang[1,2], **George W. Booz**[1], **Qing Yu**[3], **Xiaochen He**[1], **Shaoxun Wang**[1], and **Fan Fan**[1]

[1]Department of Pharmacology and Toxicology, University of Mississippi Medical Center Jackson, Mississippi, USA

[2]Department of Urology, Zhongshan Hospital, Fudan University, Shanghai, China

[3]Department of Nephrology, Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Abstract

20-HETE is a cytochrome P450-derived metabolite of arachidonic acid that has both pro- and anti-hypertensive actions that result from modulation of vascular and kidney function. In the vasculature, 20-HETE sensitizes vascular smooth muscle cells to constrictor stimuli and increases myogenic tone. By promoting smooth muscle cell migration and proliferation, as well as by acting on the vascular endothelium to cause endothelial dysfunction, angiotensin converting enzyme (ACE) expression, and inflammation, 20-HETE contributes to adverse vascular remodeling and increased blood pressure. A G protein-coupled receptor was recently identified as the effector for the vascular actions of 20-HETE. In addition, evidence suggests that 20-HETE contributes to hypertension *via* positive regulation of the renin-angiotensin-aldosterone system, as well as by causing renal fibrosis. On the other hand, 20-HETE exerts anti-hypertensive actions by inhibiting sodium reabsorption by the kidney in both the proximal tubule and thick ascending limb of Henle. This review discusses the pro- and anti-hypertensive roles of 20-HETE in the pathogenesis of hypertension-associated renal disease, the association of gene polymorphisms of cytochrome P450 enzymes with the development of hypertension and renal end organ damage in humans, and 20-HETE related pharmaceutical agents.

Keywords

Cytochrome P450; 20-HETE; hypertension; hypertensive nephropathy; vascular function; sodium transport; genetic polymorphisms

Send Correspondence to: Fan Fan, M.D., M.S., University of Mississippi Medical Center, Department of Pharmacology and Toxicology, 2500 N. State Street, Jackson, MS 39216, Ph: 601-984-1553, Fax: 601-984-1637, ffan@umc.edu.

CONFLICT OF INTEREST

None.

1. Introduction

It has long been recognized that arachidonic acid (AA) is metabolized by cyclooxygenase (COX) and lipoxygenase (LOX) to produce 5-, 12-, and 15-hydroxyeicosatetraenoic acids, leukotrienes, prostacyclin, and prostaglandins. These metabolites modulate renal function, vascular tone, and inflammatory responses (Fan et al., 2016; Fan et al., 2015b; Roman, 2002). However, a third pathway for the metabolism of AA exists in some tissues like kidney and liver, where AA is also metabolized by cytochrome P450 (CYP) enzymes into epoxyeicosatrienoic acids (EETs) and hydroxyeicosatetraenoic acids (HETEs) (Capdevila et al., 1981; McGiff and Quilley, 1999). Notably, 20-hydroxy-5, 8, 11, 14-eicosatetraenoic acid (20-HETE) is the metabolite of ω-hydroxylation of AA formed by enzymes of the CYP4A and CYP4F families (Fan et al., 2016; Fan et al., 2015b; Roman, 2002). Once produced, 20-HETE can be catalyzed by alcohol dehydrogenase (ADH) to the carboxylic acid, which is further metabolized by β-oxidation (Collins et al., 2005; Kaduce et al., 2004). In addition, 20-HETE is also metabolized by epoxygenases, COX, and LOX (Hill et al., 1992; Rosolowsky et al., 1996). After its conjugation with UDP-glucuronosyltransferases, 20-HETE can be excreted in the urine (Jarrar et al., 2014).

The isoforms of CYP enzymes that are responsible for the production of 20-HETE are different among species. CYP4A11, −4F2, and −4F3 are the isoforms that contribute to the production of 20-HETE in humans (Gainer et al., 2005; Hirani et al., 2008; Lasker et al., 2000; Powell et al., 1998). Among these isoforms, CYP4F2 is primarily responsible for the formation of 20-HETE in the kidney (Powell et al., 1998), and CYP4F3 is mainly expressed in polymorphonuclear leukocytes (PMNs) (Rosolowsky et al., 1996). CYP4A1, −4A2, −4A3, −4A8, −4F1, and −4F4 are the 20-HETE producing isoforms in rats (Kawashima et al., 1997; Kikuta et al., 1999; Nguyen et al., 1999; Williams et al., 2012; Xu et al., 2004). Among them, CYP4A1 exhibits the greatest catalytic activity (Xu et al., 2004). In mice, CYP4A10, −4A12a, −4A12b, and −4A14 are constitutively expressed, but only CYP4A12a is able to metabolize AA to 20-HETE (Dordea et al., 2016; Holla et al., 2001; Muller et al., 2007; Wu et al., 2013). However, unlike CYP4A10 and CYP4A14, CYP4A12 expression is weakly induced by fibrates and is also expressed differently in the tissues of male versus female mice (Holla et al., 2001). It should be noted that CYP4A genes are found in a single cluster on the same chromosome suggesting gene duplication. There are four genes of the 4A family in mice, rats, rabbits, and dogs. Man is the exception with only 2 isoforms and, unlike other species, has two related CYP4F genes on different chromosomes that produce 20-HETE. This could have occurred during a crossover event in evolution. Within the kidney, 20-HETE is expressed in pre-glomerular arterioles, glomeruli, proximal convoluted tubules, and pars recta. Of note, 20-HETE is the primary metabolite of AA in the thick ascending loop of Henle (TALH) in the nephron.

Recently, the first 20-HETE receptor was identified (Garcia et al., 2017). It was reported that 20-HETE affects vascular function by binding to the Gq protein-coupled receptor GPR75, which previously was identified as a receptor for the chemokine CCL5 (RANTES) (Ignatov et al., 2006; Liu et al., 2013). In endothelial cells, 20-HETE acts to impair vasodilation and increase vasoconstrictive signaling. Binding of 20-HETE to GPR75 causes dissociation of the $G\alpha_{q/11}$ subunit, produces inositol trisphosphate (IP_3), increases intracellular Ca^{2+}, and

activates MAPK. These signaling events ultimately lead to endothelial dysfunction as marked by deceased nitric oxide (NO) and increased reactive oxygen species due to uncoupling and/or loss of endothelial nitric oxide synthase (eNOS) (Fig. 1). 20-HETE also activates NF-κB signaling, which results in increased angiotensin-converting enzyme (ACE) expression that favors formation of hypertensive angiotensin II (Ang II). As discussed elsewhere (Fan and Roman, 2017), 20-HETE may also cause endothelial dysfunction and ACE expression *via* transactivation of the epidermal growth factor receptor (EGFR) (not shown).

In vascular smooth muscle cells (VSMCs), GPR75 activation is linked to protein kinase C (PKC)-mediated phosphorylation of the β subunit of the large conductance calcium-and voltage-activated potassium (BK) channels, which inhibits BK channel activity and causes vasoconstriction (Garcia et al., 2017) (Fig. 1). GPR75 may explain the actions of 20-HETE in VSMCs and endothelial cells; however, this remains to be verified in proximal tubular and TALH cells, and to be determined whether GPR75 is the only 20-HETE receptor or whether others will be identified (Fan and Roman, 2017).

As discussed in our review and summarized in Table 1, 20-HETE has both pro- and anti-hypertensive actions. The former are attributed to its aforementioned actions on the endothelial cells and VSMC of both the renal and peripheral vasculature. The anti-hypertensive and extravascular actions of 20-HETE result from natriuretic and diuretic actions arising from inhibition of sodium reabsorption in both the proximal tubule (PT) and TALH. Confoundingly, the intra-renal, anti-hypertensive actions of 20-HETE are opposed by the renin-angiotensin-aldosterone-system (RAAS), which may be activated by 20-HETE.

2. Role of 20-HETE in promoting hypertension

20-HETE acts as a potent vasoconstrictor of VSMC by multiple means (Fig. 1). It blocks BK channel activity, leading to a fall in membrane potential, which enhances calcium entry *via* voltage-gated L-type Ca^{2+} channels and transient receptor potential cation channel 6 (TRPC6), resulting in vasoconstriction. (Fan et al., 2013b; Gebremedhin et al., 1998; Roman, 2002; Williams et al., 2010). 20-HETE activates mitogen-activated protein kinases (MAPKs) (Garcia et al., 2016), PKC (Sun et al., 1999), Rho-kinase/ROCK, and tyrosine-kinases (Parmentier et al., 2001b; Sun et al., 1999), which lead to VSMC contraction either *via* increased intracellular Ca^{2+} or by enhanced phosphorylation of contractile elements (Fig. 1) (Fan et al., 2013b; Gebremedhin et al., 1998; Roman, 2002; Williams et al., 2010).

Elevations in transmural pressure promote 20-HETE production and inhibition of 20-HETE synthesis impairs myogenic reactivity in renal arteries (Gebremedhin et al., 2000). 20-HETE enhances vascular response to stretch (Gao et al., 2008; Goodman et al., 2003; Nakayama et al., 2003), Ang II (Fan et al., 2013b; Lima et al., 2013), endothelin 1 (Berg, 2016; Oyekan et al., 1999), vasopressin (Omata et al., 1992a), serotonin (Cambj-Sapunar et al., 2003; Roman et al., 2006), and contributes to oxidative stress (Dunn et al., 2008; Hou et al., 2010; Singh et al., 2007), endothelial dysfunction (Dunn et al., 2008), and inflammation (Hoopes et al., 2015; Miyata and Roman, 2005), all of which alter renal hemodynamics (enhance afferent

arteriole autoregulation and decrease renal blood flow) and increase peripheral vascular resistance, thereby promoting development of hypertension.

The first implication of the relationship between 20-HETE and hypertension was reported in 1989 (Sacerdoti et al., 1989). The investigators found that selective depletion of renal cytochrome P450 and AA metabolites prevented elevated blood pressure in the Spontaneously Hypertensive Rat (SHR). Direct evidence was then provided in 1991 that SHR elevated in the kidney in SHR (Ishizuka et al., 2004; Kroetz et al., 1997; Omata et al., 1992a; Omata et al., 1992b; Schwartzman et al., 1996). Therefore, it seems that the hypertensive phenotype in the SHR is due to elevated renal 20-HETE formation and, thus, it would be expected that inhibition of renal production of 20-HETE would attenuate the degree of hypertension in this model. Indeed, induction of heme oxygenase (HO) reduced (Goodman et al., 2003) or blocked formation of 20-HETE and slowed development of hypertension in male (Gebremedhin et al., 1993; Imig et al., 1993; Kroetz et al., 1997; Omata et al., 1992a; Schwartzman et al., 1996; Zhang et al., 2005) and post-menopausal female SHR (Yanes et al., 2011). Administration of dihydrotestosterone (DHT) in both male and female Sprague Dawley rats upregulated 20-HETE production in renal parenchymal and vascular tissues by elevating expression of CYP4A8 through the androgen receptor, and promoted development of hypertension (Singh et al., 2007; Singh and Schwartzman, 2008; Wu and Schwartzman, 2011).

The relationship of 20-HETE and hypertension was also investigated in hypertensive mouse models. Upregulation of CYP4A12 by exogenous DHT, or as is seen in nitric oxide (NO) receptor deficient sGCα1 (−/−) mice, produced 20-HETE-dependent hypertension and vascular dysfunction (Dordea et al., 2016; Muller et al., 2007; Wu et al., 2013). CYP4A14 is highly expressed in female mice (Heng et al., 1997; Holla et al., 2001; Muller et al., 2007), but knockout of CYP4A14 (Fidelis et al., 2010; Holla et al., 2001; Muller et al., 2007) induced hypertension in male mice only. This was associated with an increase in plasma testosterone levels and renal CYP4A12 expression and 20-HETE formation, as well as reduced renal production of NO (Fidelis et al., 2010). These findings suggest that CYP4A14 may produce a metabolite that inhibits testosterone production. Hypertension in this model was reversed by castration (Holla et al., 2001) and the elevation in renal perfusion pressure to phenylephrine was blunted by an inhibitor of 20-HETE synthesis (Fidelis et al., 2010). More recent studies indicate that knock-in of human CYP4A11 (Savas et al., 2016) and CYP4F2 (Cai, 2009; Fava et al., 2009; Liu et al., 2009) in mice enhanced renal production of 20-HETE and promoted development of hypertension. Levels of 20-HETE were also elevated in various tissues including kidneys and endothelial cells in endothelial-specific human CYP4F2 transgenic mice (Cheng et al., 2014); however, blood pressure was not altered in this model. These studies indicate that increased formation of 20-HETE is associated with elevations in blood pressure in male, but not female mice, since it is linked to elevations in testosterone-induced CYP4A12 expression. The relationship between these findings and the influence of 20-HETE on the development of hypertension in man remain to be determined.

3. Impact of 20-HETE on hypertensive vascular remodeling and nephropathy

20-HETE plays a pro-fibrotic role in hypertensive nephropathy. In streptozotocin (STZ) treated diabetic CYP4A14 KO mice, the increased renal 20-HETE production (due to increased plasma testosterone levels and consequent induction of CYP4A12 gene expression) was associated with hypertension (Gangadhariah et al., 2015; Holla et al., 2001) and exacerbated renal injury. Increased urinary protein excretion, expansion of mesangial and glomerular basement membranes, and deposition of glomerular matrix were observed (Gangadhariah et al., 2015; Holla et al., 2001). These results are consistent with previous studies that enhanced CYP4A/20-HETE levels accompanied elevated reactive oxygen species production in cultured mouse podocytes (Eid et al., 2009) and rat proximal tubular epithelial cells (Eid et al., 2013). Increased expression of 20-HETE in STZ-treated mice and rats was also associated with increased reactive oxygen species generation, NADPH oxidase activity (Eid et al., 2009), transforming growth factor-β1 (TGF-β1) and fibronectin expression, as well as glomerular matrix formation, podocyte apoptosis, and urinary protein excretion (Eid et al., 2009; Elmarakby et al., 2013).

Vascular remodeling is one of the key pathophysiological processes in hypertension and is related to an increase in the media-to-lumen ratio of small arteries and arterioles, leading to vascular hyperactivity to constrictor stimuli and enhanced peripheral resistance (Renna et al., 2013). The renal expression of 20-HETE is increased in SHR, and 20-HETE is involved in the augmented renal vascular reactivity to Ang II, which results in profound vascular remodeling (Gebremedhin et al., 1993). 20-HETE also contributes to vascular hypertrophy in a CYP4A12 transgenic mouse independent of the increase in mean arterial pressure (Wu et al., 2013). These studies demonstrate that 20-HETE plays a role in vascular remodeling, a process that involves activation of multiple vascular components such as endothelium and VSMCs, and deposition of extracellular matrix (ECM) and basement membrane (McGrath et al., 2005).

Besides promoting proliferation of VSMCs (Fan et al., 2016; Orozco et al., 2013), which has been implicated in restenosis, 20-HETE also stimulates mitogenesis of endothelial (Chen et al., 2012; Cheng et al., 2014; Guo et al., 2007) and renal epithelial cells (Akbulut et al., 2009). 20-HETE-induced endothelial cell proliferation may contribute to atherosclerotic neovascularization/angiogenesis and related plaque instability and rupture (Chen et al., 2012; Moreno et al., 2006; Sun, 2014), events that are associated with and exacerbated by hypertension (Picariello et al., 2011). Renal epithelial cell proliferation has significant implications for polycystic kidney disease (PKD) (Park et al., 2009), which commonly is associated with hypertension, although the mechanism is unclear. 20-HETE is stimulated by pro-angiogenic factors such as hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) to promote cell migration and proliferation (Chen et al., 2014; Muthalif et al., 1998; Parmentier et al., 2001a; Stec et al., 2007a). Moreover, 20-HETE induces VEGF expression that drives endothelial cell proliferation in a signaling cascade involving apocynin-insensitive reactive oxygen species production and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) activation

(Chen et al., 2014; Guo et al., 2007). In kidney epithelial cells, 20-HETE was found to activate the mitogenic Raf/MEK/ERK and protein kinase B (PKB/Akt) signaling pathways *via* c-Src-mediated transactivation of EGFR (Akbulut et al., 2009). Whether 20-HETE also acts on renal epithelial cells through the same GPR75 receptor as on endothelial and VSMCs remains to be determined (Fan and Roman, 2017; Garcia et al., 2017). Overall, these studies suggest that 20-HETE plays a role in vascular or kidney remodeling, which might be associated with its effect to promote angiogenesis and endothelial or renal epithelial cell proliferation.

20-HETE has also been known to play a role in promoting vascular inflammation. Arteries that were treated with a biosynthesis inhibitor of 20-HETE, HET0016 resulted in attenuation of reactive oxygen species and vascular nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, and reduction of vascular inflammation, which was associated with decreases in pro-inflammatory cytokine expression, such as tumor necrosis factor-alpha (TNFα), interleukin-1 beta (IL-1β), and IL-6 (Toth et al., 2013). 20-HETE has also been found to induce expression of multiple adhesion molecules such as monocyte chemotactic protein 1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion protein 1 (VCAM-1) in the vasculature (Hoopes et al., 2015). The adhesion molecules increase vascular inflammation by recruiting monocytes and macrophages to the vascular wall.

4. Interplay between 20-HETE and the renin-angiotensin-aldosterone system (RAAS) in hypertension and hypertensive nephropathy

The renin-angiotensin-aldosterone system, which acts either in a systemic endocrine or in a local paracrine/autocrine fashion, plays an important role in cardiovascular homeostasis (Harrison-Bernard, 2009). Ang II is the central bioactive component of the RAAS and exerts a crucial role in regulating vascular myogenic tone in normal physiology, as well as in the pathogenesis of hypertension and other cardiovascular disorders (Mehta and Griendling, 2007; Paul et al., 2006). Reduced arterial blood pressure, a decrease in sodium load, or activation of the sympathetic nervous system (SNS) all stimulate renin secretion (Paul et al., 2006). Renin cleaves angiotensinogen to produce Ang I, which is further converted to Ang II by ACE (Roman et al., 2016). Tissue-specific renin- or ACE-independent routes for Ang II formation have also been identified (Forrester et al., 2018). In addition, evidence has suggested that the kidney expresses all necessary components for Ang II formation and thus possesses a local renin-angiotensin-system, although recent reports question the intra-renal origins of angiotensinogen and other system components (Roman et al., 2016).

Emerging evidence suggests a complex interplay between 20-HETE and the RAAS. A positive feedback between 20-HETE and Ang II exists and contributes to vasoconstriction and hypertension (Alonso-Galicia et al., 2002; Chu et al., 2000; Croft et al., 2000; Fan et al., 2013b; Joly et al., 2006; Park et al., 2001). Ang II increases renal production of 20-HETE (Alonso-Galicia et al., 2002), while the RAAS is suppressed in a salt-sensitive hypertensive rat with decreased expression of glomerular CYP4A1 (Ito and Roman, 1999). Chronic deoxycorticosterone acetate (DOCA)-salt treatment suppresses the systemic renin-

angiotensin system, and 20-HETE expression was reduced in a DOCA-salt hypertensive mouse model (Honeck et al., 2000); however, 20-HETE levels were elevated in the DOCA-salt hypertensive rat (Oyekan et al., 1999), perhaps implicating a direct role for the mineralocorticoid receptor in this model.

Recent studies demonstrated that 20-HETE activates the RAAS in part by inducing vascular expression of ACE downstream of NF-κB activation (Cheng et al., 2012; Garcia et al., 2016; Sodhi et al., 2010); however, 20-HETE-mediated microvascular remodeling in hypertension did not fully rely on ACE activity in the vascular endothelium (Cheng et al., 2012; Garcia et al., 2015). Moreover, increased 20-HETE may not necessarily be associated with enhanced RAAS activity. For instance, fenofibrate treatment induced intrarenal 20-HETE production, thereby attenuating hypertension in an Ang II-dependent mouse model *via* enhanced sodium excretion (see below, Role of 20-HETE in preventing hypertension and hypertensive nephropathy) (Vera et al., 2005). In contrast, fenofibrate increased renal production of 20-HETE and plasma renin activity in both Stroke-Prone Spontaneously Hypertensive Rats (SHRSP) and salt-sensitive hypertensive Dahl S rats (Shatara et al., 2000). In a human-derived 20-HETE-producing CYP4A11 transgenic mouse, 20-HETE enhanced the production of renal angiotensinogen and activation of Ang II type 1 (AT1) receptor and this enhancement paralleled an increase in plasma potassium level and in activities of the sodium chloride co-transporter (NCC) and serum/glucocorticoid regulated kinase 1 (SGK1), even though plasma aldosterone, Ang II, and renin activities remained unchanged (Savas et al., 2016). This investigation suggests that 20-HETE may contribute to hypertension and its complications *via* upregulation of sodium transport in the distal nephron secondary to increased activity of RAAS.

Hypertension in the SHR is dependent on both the RAAS and 20-HETE and is associated with elevated sympathetic tone. Little is known as to whether 20-HETE interacts with Ang II to increase sympathetic activity or potentiates the effects of norepinephrine at the level of smooth muscle. More studies are necessary to elucidate whether the link between 20-HETE and RAAS is mediated solely *via* changes in vascular reactivity, sodium retention activation of the SNS, or *via* combinational effects.

5. Hypertensive actions of 20-HETE summarized

20-HETE promotes hypertension by several means involving both the peripheral vasculature and kidney. It serves as an autocrine second messenger and enhances the vascular response to constrictor stimuli in peripheral VSMCs, as well as renal afferent arteries. It also promotes endothelial dysfunction, and induces vascular inflammation, and RAAS activation. Furthermore, 20-HETE promotes renal oxidative stress and fibrosis, directly or *via* apoptosis of kidney cells. These factors, in our opinion, mainly account for the role of 20-HETE in promoting hypertension and contributing to hypertension associated renal end organ damage.

6. Role of 20-HETE in preventing hypertension and hypertensive nephropathy

On the other hand, 20-HETE prevents hypertension by inhibiting sodium reabsorption and promoting natriuresis (Fig. 2). It inhibits Na^+-K^+-ATPase activity and internalizes sodium-hydrogen exchanger 3 (NHE3) in the PT, thereby diminishing sodium transport in renal tubules (Capdevila et al., 2003; Fan et al., 2016; Fan et al., 2015b; Roman, 2002). In the TALH, 20-HETE inhibits Na^+ reabsorption and induces natriuresis by several means: 20-HETE a) inhibits the basolateral Na^+/K^+-ATPase and luminal Na^+-K^+−$2Cl^−$ cotransporter; and b) inhibits both the luminal 70 pS K^+ channel responsible for K^+ back-leak that sustains cotransporter activity and the basolateral 50 pS K^+ channel that affects cotransporter activity by controlling the driving force for $Cl^−$ cellular exit (Fan et al., 2016; Fan et al., 2015b; Gu and Wang, 2002; Roman, 2002; Yu et al., 2007)

Induction of renal formation of 20-HETE with fibrates attenuates, rather than promotes, high blood pressure in SHRSP (Shatara et al., 2000) or SHR (Hou et al., 2010). The divergent results can be understood by the observation that fenofibrate increases renal 20-HETE and natriuresis, but does not alter vascular 20-HETE, because blood vessels do not express peroxisome proliferator-activated receptor alpha (PPAR-α) (Vera et al., 2005). This finding suggests that the 20-HETE produced in renal tubules may contribute to the blood pressure-lowering effects of fibrates treatment in Ang II-dependent hypertension without affecting or overweighting its effects on vascular tone. This viewpoint is supported by more recent studies in the Dahl S rats.

The Dahl S rat is a low renin, salt-sensitive model of hypertension due to enhanced reabsorption of sodium in the PT and TALH. In the Dahl S rat, reduced levels of CYP4A and 20-HETE are associated with rapid development of hypertension with salt diet, impaired pressure natriuresis relationship, and abnormal sodium transport in the kidney (Williams et al., 2008; Williams et al., 2007b). These rats also have impaired renal microvascular function (Fan et al., 2013a; Ge et al., 2014). These findings are similar to another study in SHR, whereby the induction of 20-HETE with fibrates attenuated hypertension and reduced proteinuria (Shatara et al., 2000). Transfer of chromosome 5 which contains 4 isoforms of CYP4A enzymes from normotensive Lewis or Brown Norway (BN) strains or transfer of a single BN CYP4A1 gene to the Dahl S rat prevented development of hypertension, improved natriuresis, and rescued the impaired myogenic response of both renal and cerebral arterioles (Fan et al., 2013a; Fan et al., 2014; Ge et al., 2014; Murphy et al., 2013; Williams et al., 2012; Williams et al., 2008).

Dahl S rats exhibit a deficiency in the formation of 20-HETE (Fan et al., 2015a; Williams et al., 2012; Williams et al., 2008), an elevation in glomerular capillary pressure, and an increase in permeability of the glomerulus to albumin, which are associated with enhanced renal TGF-β1 expression and development of hypertension-induced chronic kidney disease (Fan et al., 2015a; Williams et al., 2012; Williams et al., 2008). These rats also have impaired renal myogenic and TGF responses, increased renal interstitial pressure in response to elevation of renal perfusion pressure, and a reset of pressure-natriuresis (Fan et al., 2013a; Ge et al., 2014; Ren et al., 2014). The renal protective effect of 20-HETE was confirmed in

transgenic Dahl S rats in which the CYP4A gene(s) was knocked in or overexpressed (Murphy et al., 2012; Murphy et al., 2013; Williams et al., 2012; Williams et al., 2008). These rats exhibited diminished albumin permeability, rescued glomerular filtration rate (GFR), and attenuated glomerular capillary leakage (Dahly-Vernon et al., 2005; McCarthy et al., 2005; Williams et al., 2007b). More evidence was recently provided that 20-HETE, a physiological substrate of ADH in podocytes, protected the glomerular permeability barrier in ethanol treated mice in which CYP4A12a was upregulated by blocking cytoskeletal derangement and production of superoxide (McCarthy et al., 2015).

The available evidence suggests that elevated 20-HETE induces hypertension, but prevents renal injury due to elevation of renal vascular tone in models associated with involvement of RAAS. Results with a 20-HETE inhibitor in Lyon hypertensive rats further support this conclusion (Lantelme et al., 1997; Messer-Letienne et al., 1999; Williams et al., 2007a). Deficiencies in 20-HETE in the kidney increase tubular sodium reabsorption and promote salt-sensitive hypertension and renal injury due to decreased renal vascular reactivity.

7. Human genetic studies

In humans, CYP4F2 is the most potent isoform, followed by CYP 4A11, among the predominant 20-HETE producing enzymes: CYP4A11, −4A22, −4F2, and −4F3 (Gainer et al., 2005; Hirani et al., 2008; Lasker et al., 2000; Powell et al., 1998). A number of single nucleotide polymorphisms (SNPs) in the CYP4F2 (V433M, G421C, GA/AA) and CYP4A11 (T8590C) genes have been reported to play a role in the development of hypertension in several cohorts (Gainer et al., 2008; Laffer et al., 2008; Liu et al., 2008; Liu et al., 2006; Mayer et al., 2005; Ward et al., 2008; Williams et al., 2011). Among these SNPs, the V433M variant (Stec et al., 2007b) in CYP4F2 and the T8590C variant (Gainer et al., 2005) in CYP4A11 decrease the activities of these enzymes, and the later SNP is also associated with the pathogenesis of salt-sensitive hypertension (Williams et al., 2007b; Yanes et al., 2011). Other reports showed that the renal excretion of 20-HETE-glucuronide is elevated in hypertensive patients with CYP4F2 SNPs (Liu et al., 2008; Ward et al., 2008). These authors suggested that 20-HETE might promote hypertension by enhancing renal vasoconstriction, but this hypothesis remains to be validated because renal blood flow (RBF) or GFR was not measured in these hypertensive patients. Moreover, recent studies have indicated that urinary glucuronide conjugate-20-HETE is not of renal origin, since the amount of the conjugated form of 20-HETE is higher in the plasma than in urine when the fractional excretion is <1% (Dreisbach et al., 2014).

Overall, these studies indicate that 20-HETE plays an important role in the development of hypertension in humans. However, more studies are needed to determine to what extent changes in 20-HETE production contribute to the antihypertensive effects of diuretics, ACE inhibitors, AT1 receptor antagonists, and other antihypertensive agents.

8. The development of 20-HETE related pharmaceutical agents

Along the way in studying the role of 20-HETE in various pathological processes, a variety of 20-HETE-related pharmaceutical agents have been synthesized (Williams et al., 2010; Yu

et al., 2004) (Fig. 3). These include CYP inhibitors and inducers, and 20-HETE agonists and antagonists. In the early period, several specific inhibitors of CYP4A enzymes were synthesized and used for evaluating the role of CYP metabolites of AA, such as 1-aminobenzotriazole (ABT) and 17-octadecynoic acid (17-ODYA) (Knickle and Bend, 1992; Mathews et al., 1985; Zou et al., 1994). However, they were not satisfactory because they are not specific and could also block the formation of EETs (Knickle and Bend, 1992; Maier et al., 2000; Mathews et al., 1985; Zou et al., 1994), a group of AA metabolites with effects on vascular function generally opposite to 20-HETE. The second generation of inhibitors to specifically block formation of 20-HETE, 12, 12-dibromododec-11-enamide (DBDD) and N-methylsulfonyl-12, 12-dibromododec-11-enamide (DDMS), were synthesized by Dr. Falck (Alonso-Galicia et al., 1997; Wang et al., 1998). These compounds proved to completely inhibit formation of 20-HETE at a concentration of 10 μM, whereas the activity of EETs was only reduced by 10–20% under the same condition (Alonso-Galicia et al., 1997). The main limitation of these agents is their fatty acid property with a rather high albumin-binding rate in the plasma, which restricts distribution of these compounds to targeted tissues.

A new inhibitor of CYP4A enzymes, N-hydroxy-N'-(4-n-butyl-2-methylphenyl) formamidine (HET-0016) was created (Miyata et al., 2001). This compound could inhibit formation of 20-HETE in a potent and selective way for its IC_{50} is only 8.9 nM and it has no effect on other enzymes that are responsible for AA metabolism such as COX, epoxygenase, LOX, or other CYP isoforms that are not involved in producing 20-HETE (Miyata et al., 2001). Later, a more potent and selective HET-0016 analog, TS011 was developed (Williams et al., 2010). In general, HET-0016 is commercially available and is the most widely used inhibitor of 20-HETE synthesis.

A number of analogues of 20-HETE were created by Dr. Falck. Drs. Falck and Roman found that these compounds could act either as agonists or antagonists of 20-HETE by interacting with a putative 20-HETE receptor in vascular smooth muscle (Alonso-Galicia et al., 1998; Roman, 2003; Yu et al., 2004). The extensively used agonists of 20-HETE are 20-hydroxyeicosa-5(Z), 14(Z)-dienoic acid (5, 14–20-HEDE or WIT-003), and N-[20-hydroxyeicosa-5(Z), 14(Z)-dienoyl] glycine (5, 14–20-HEDGE) (Akbulut et al., 2009; Regner et al., 2009; Renic et al., 2012), while the most effective analogue to block the vasoconstrictor response to 20-HETE appears to be 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid (6,15–20-HEDE or WIT-002) (Alonso-Galicia et al., 1999; Frisbee et al., 2001; Gebremedhin et al., 2000). However, the use of these compounds as drugs are limited because of protein binding, short half-life, and poor solubility.

Very recently, a novel water-soluble 20-HETE antagonist, 2, 5, 8, 11, 14, 17-hexaoxanonadecan-19-yl 20-hydroxyeicosa-6(Z), 15(Z)-dienoate (20-SOLA) was synthesized. Administration of 20-SOLA was found to reduce blood pressure as a result of increased natriuresis in hypertensive CYP4A14 KO mice (Pandey et al., 2017). This model of androgen-driven hypertension is associated with both 20-HETE-induced vasoconstriction and renal hypoperfusion, as well as excessive sodium and volume reabsorption due to Ang II-induced upregulation of NHE3 in the proximal tubule and NCC in the distal convoluted tubule. Increased renal Ang II is likely attributed to 20-HETE-driven vascular ACE or renal

angiotensinogen expression. Thus, the anti-hypertensive actions of the 20-SOLA in this hypertensive model may have resulted from increased glomerular filtration and attenuation of the RAAS. Finally, Dr. Eric F. Johnson reported a more soluble 20-HETE antagonist than 6, 15–20-HEDE, sodium (S)-2-((6Z, 15Z)-20-hydroxyicosa-6, 15-dienamido)-succinate (AAA), which contributed to the reduced blood pressure in human CYP 4A11 transgenic mice (Savas et al., 2016). These compounds appear to be the most likely candidates for drug development for treatment of myocardial infarction, stroke, chronic kidney disease, neovascularization and other 20-HETE-associated cardiovascular complications.

9. Perspectives

In summary, 20-HETE plays an important role in the control of blood pressure. The regulation depends on the balance of 20-HETE's pro-hypertensive effects on the vasculature and anti-hypertensive effects in the kidney. Identification of genetic variants in the 20-HETE-producing enzymes or development of drugs targeting the production of 20-HETE could provide useful information for the early diagnosis, prevention, and treatment of hypertension and hypertension-related tissue injuries. Additional research into the effect of high salt diet on vascular and renal 20-HETE and CYP isoform expression levels is needed to resolve this issue (Frisbee et al., 2000; Roman, 2002; Walkowska et al., 2015), as well as the role of the gut microbiota. A recent study showing rhythmic expression of EETs in the rat brain and vasculature would suggest that vascular and renal levels of 20-HETE may be under circadian control as well (Carver et al., 2014). Finally, therapeutic approaches based on genetic manipulations, such cell-targeted miRNA delivery, to separate the renal from vascular effects of 20-HETE or its synthesis, are needed and may prove beneficial for treating hypertension.

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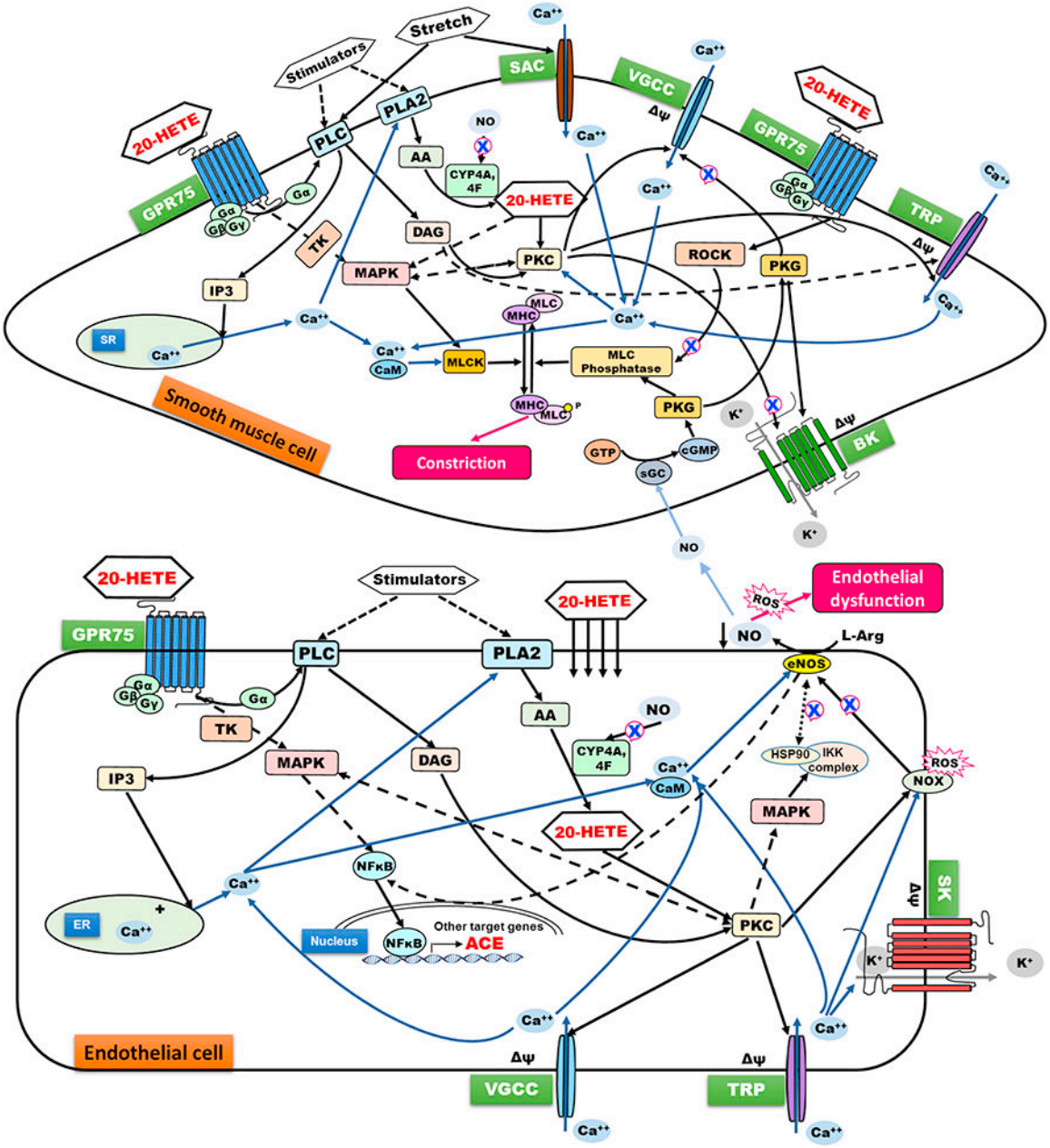


Figure 1. Overview of signaling events in endothelial and vascular smooth muscle cells contributing to hypertension.

Stretch or vasoconstrictors increase intracellular Ca^{2+} and activate PLA2 to generate 20-HETE, which can act either intracellularly to stimulate PKC or extracellularly via the $G\alpha_{q/11}$ protein-coupled receptor GPR75 (or other yet-to-be identified GPCR). Overall, 20-HETE antagonizes the actions of the vasodilator NO, which can down-regulate levels of 20-HETE-forming CYPs. In VSMC (top figure), 20-HETE and GPR75 couple to increase intracellular Ca^{2+} and contraction by 1) activation of MLCK (downstream of Ca^{2+}/calmodulin or MAPK), (2) ROCK-mediated inhibition of MLC phosphatase, as well as by PKC-mediated (3a) activation of VGCC, (3b) phosphorylation of contractile proteins, and (3c) inhibition of BK. In the endothelium (bottom figure), 20-HETE-mediated activation of GPR75 promotes

loss of NO and endothelial dysfunction by uncoupling eNOS, activating NOX, and disrupting eNOS-HSP90 association, thus promoting reactive oxygen species formation. 20-HETE also induces expression of angiotensin-converting enzyme (ACE), thereby increasing levels of the vasoconstrictor Ang II. 20-HETE promotes endothelial inflammation by increasing expression of adhesion molecules, cytokines, and chemokines for leukocytes. ACE, angiotensin converting enzyme; BK, calcium-activated potassium channel; CaM, calmodulin; DAG, diacylglycerol; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; GPCR, G-protein coupled receptor; HSP90, heat shock protein 90; IP3, inositol trisphosphate; L-Arg, L-arginine; MAPK, mitogen-activated protein kinases; MHC, myosin heavy chain; MLC, myosin light chain; MLCK, myosin light-chain kinase; NFκB, nuclear factor κ-light-chain-enhancer of activated B cells; PKC, protein kinase C; PKG, protein kinase G; PLA2, phospholipase A2; PLC, phospholipase C; ROCK, Rho-activated kinase; SAC, stretch-activated calcium channel; SK, small conductance calcium-activated potassium channels; sGC, soluble guanylyl cyclase; SR, sarcoplasmic reticulum; TK, tyrosine kinases; TRP, transient receptor potential channels; VGCC, voltage-gated calcium channel. See text and (Fan and Roman, 2017) for additional details.

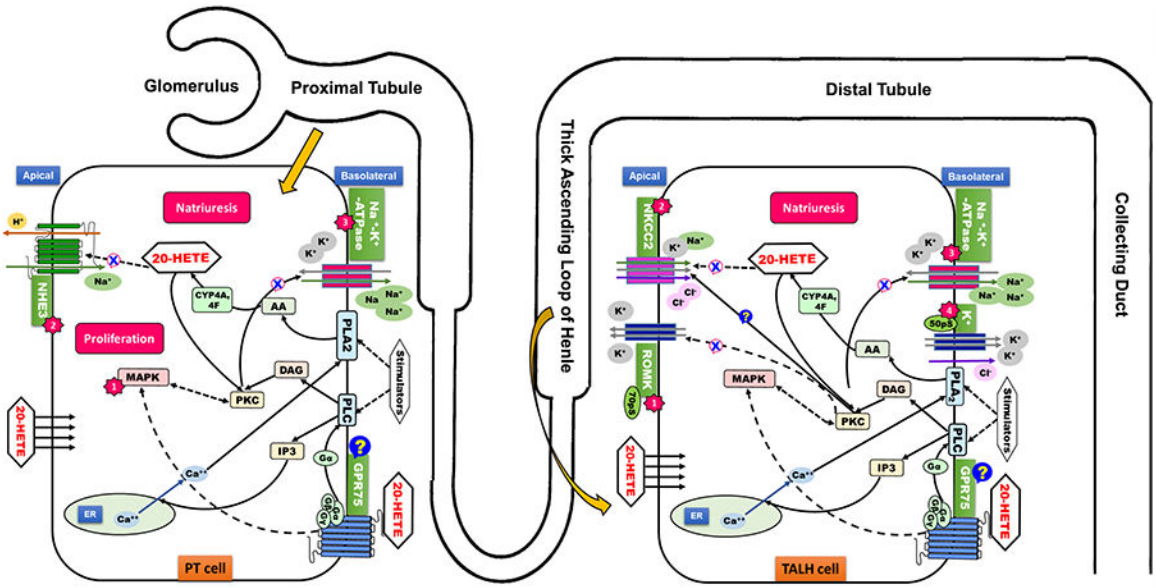


Figure 2. The effect of 20-HETE on different segments of the nephron to enhance natriuresis.

20-HETE is actively produced from PLA2-mediated formation of AA in proximal tubular cells and TALH cells by hormonal and stress stimulators downstream of PLC-mediated increases in intracellular Ca^{2+}. 20-HETE may act intracellularly or *via* GPR75. In proximal tubular cells, 20-HETE promotes cellular proliferation by activation of PKC/MAPK mediated signaling pathway (1). 20-HETE also internalizes NHE3 *via* an undefined process (2) and inhibits activity of Na^+-K^+-ATPase by PKC-mediated phosphorylation (3), thereby diminishing sodium transport from the apical (luminal) to basolateral side of proximal tubule cells. In TALH cells, 20-HETE inhibits the apical NKCC2 cotransporter (2) and basolateral Na^+-K^+-ATPase (3) to prevent sodium reabsorption from the renal tubular lumen into the basolateral space. 20-HETE also inhibits the 70pS ROMK located on the apical side (1) and the 50pS ROMK located on the basolateral side (4), which normally contribute to NKCC2 cotransporter activity by allowing for K^+ back-leak into tubular lumen and driving Cl^- transcellular flux, respectively. All of the actions on proximal tubule cells and TALH cells by 20-HETE contribute to natriuresis and the prevention of water-sodium retention. NHE3, sodium-hydrogen antiporter 3; NKCC2, Na^+-K^+−2Cl^- cotransporter; ROMK2, renal outer medullary potassium channel 2; PLA2, phospholipase A2; PLC, phospholipase C; PKC, protein kinase C; TALH, thick ascending loop of Henle. See text and Figure Legend 1 legend for additional details.

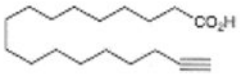
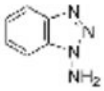
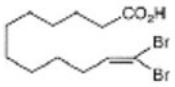
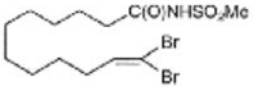
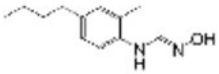
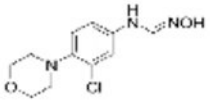
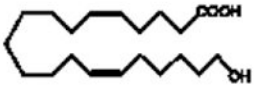
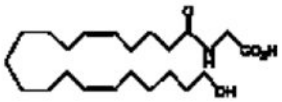
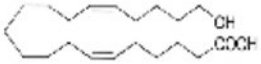
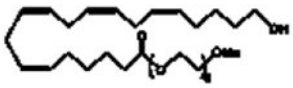
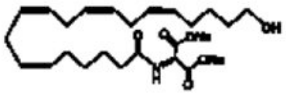
Name	Structure	Feature	Selective target
17-ODYA		suicide substrate, irreversible inhibition	20-HETE and EETs inhibitor
ABT		suicide substrate, irreversible inhibition	20-HETE and EETs inhibitor
DBDD		competitive inhibition, low bioavailability	20-HETE inhibitor
DDMS		competitive inhibition, low bioavailability	20-HETE inhibitor
HET-0016		specific and potent, commercially available	selective 20-HETE inhibitor
TS011		10 times more potent than HET-0016	selecitve 20-HETE inhibitor
5, 14-20-HEDE		poor bioavailability	20-HETE agonist
5, 14-20-HEDGE		more soluble than 5,14-20-HEDE	20-HETE agonist
6,15-20-HEDE		poor bioavailability	20-HETE antagonist
20-SOLA		orally active	20-HETE antagonist
AAA		more soluble than 20-SOLA	20-HETE antagonist

Figure 3. Development of 20-HETE-related pharmaceutical agents.

20-HETE-related pharmaceutical agents are summarized, including CYP inhibitors and inducers, and 20-HETE agonists and antagonists. Chronologically, these compounds became more potent, specific, and soluble with development. Abbreviations: 17-ODYA: 17-octadecynoic acid; ABT: 1-aminobenzotriazole; DBDD: 12, 12-dibromododec-11-enamide; DDMS: N-methylsulfonyl-12, 12-dibromododec-11-enamide; HET-0016: N-hydroxy-N'-(4-n-butyl-2-methylphenyl) formamidine; TS011: N-(3-Chloro-4-morpholin-4-yl) Phenyl-N'-hydroxyimido formamide; 5, 14–20-HEDE or WIT-003: 20-hydroxyeicosa-5(Z), 14(Z)-dienoic acid; 5, 14–20-HEDGE: N-[20-hydroxyeicosa-5(Z), 14(Z)-dienoyl] glycine; 6,15–20-HEDE or WIT-002: 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid; 20-SOLA: 2, 5, 8, 11,

14, 17-hexaoxanonadecan-19-yl 20-hydroxyeicosa-6(Z), 15(Z)-dienoate; AAA: sodium (S)-2-((6Z,15Z)-20-hydroxyicosa-6,15-dienamido)- succinate.

Table 1 -

Cell-specific actions of 20-HETE that affect blood pressure

Cell Type	↑ Blood Pressure	↓ Blood Pressure
EC	↓ NO, inflammation, ↑ACE	
VSMC	↑ contractility leading to ↓ GFR & ↑ PVR	
PT	↑Na^{2+} & H_2O reabsorption from ↑renal Ang II	↓ Na^{2+} & H_2O reabsorption
DT	↑Na^{2+} reabsorption from ↑renal Ang II	
TALH	↑Na^{2+} & H_2O reabsorption from ↑renal Ang II	↓ Na^{2+} & H_2O reabsorption

DT, distal tubule; EC, endothelial cell; PVR, peripheral vascular resistance; PT, proximal tubule; TALH, thick ascending limb of Henle.