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20-HETE: A NEW TARGET FOR THE TREATMENT OF HYPERTENSION

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Abstract

Arachidonic acid (AA) is metabolized by enzymes of the CYP4A and 4F families to 20-hydroxyeicosatetraeonic acid (20-HETE) which plays an important role in the regulation of renal function, vascular tone and the long term control of arterial pressure. In the vasculature, 20-HETE is a potent vasoconstrictor and upregulation of the production of this compound contributes to the elevation in oxidative stress, endothelial dysfunction and the increase in peripheral vascular resistance associated with some forms of hypertension. In kidney, 20-HETE inhibits Na^+ transport in the proximal tubule and thick ascending loop of Henle and deficiencies in the renal formation of 20-HETE contributes to sodium retention and the development of some salt-sensitive forms of hypertension. 20-HETE also has renoprotective actions and opposes the effects of transforming growth factor (TGF-β) to promote proteinuria and renal end organ damage in hypertension. Several new inhibitors of the synthesis of 20-HETE and 20-HETE agonists and antagonists have recently been developed. These compounds along with PPAR-α agonists that induce the renal formation 20-HETE appear to have promise as antihypertensive agents. This review summarizes the rationale for the development of drugs that target the 20-HETE pathway for the treatment of hypertension and associated cardiovascular complications.

Keywords

hypertension; 20-HETE; kidney; blood vessels; vascular tone

Introduction

Hypertension affects more than 50 million Americans and >30 billion dollars a year is spent on drugs to control high blood pressure. However, patient compliance and the high cost of drug therapy are serious problems, and blood pressure remains largely uncontrolled in 75% of the patients in North America.[1] Hypertension is one of the primary risk factors for stroke, ischemic heart disease, chronic kidney disease and it contributes to the escalating health care costs in the US. Thus, there is a great need for a better understanding of the genes and pathways that contribute to the development of hypertension and for the development of new therapies.

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Studies performed over the last 10 years have revealed that arachidonic acid (AA) is metabolized by cytochrome P450 (CYP) enzymes of the 4A and 4F families in a variety of tissues to 20-hydroxyeicosatetraeonic acid (20-HETE) and that this compound plays an important role in the regulation of vascular tone and sodium transport in the kidney. The formation of 20-HETE is altered in various models of hypertension and drugs that target the 20-HETE pathway have been reported to lower blood pressure in preclinical studies. This review summarizes the renal and vascular actions of 20-HETE, the evidence that the expression and production of 20-HETE is altered in hypertension and the therapeutic potential of drugs that target this pathway for the treatment of hypertension.

CYP mediated metabolism of AA

AA is avidly metabolized by CYP4A and 4F enzymes in the liver,[2-4] kidney,[5-10] heart,[11-12] lung,[13-16] brain[17-19] and the vasculature[17-23] to 20-HETE. There are four CYP4A isoforms (4A1, 4A2, 4A3, and 4A8) and four CYP4F isoforms (4F1, 4F4, 4F5 and 4F6) that can produce 20-HETE in various tissues in the rat. The homologous isoforms that catalyze the formation of 20-HETE in man are CYP4A11, 4F2 and 4F3.[24-26]

Many factors influence the expression of CYP enzymes of the 4A and 4F families. Fibrates induce the expression of CYP4A1 and 4A3 in the liver and kidney[27-29] but not in the blood vessels which do not express the PPARα receptor.[28] The renal production of 20-HETE is altered in diabetes,[30-31] pregnancy,[32] hepatorenal syndrome[33] and in many models of hypertension.[34-46] It is also altered by changes in sodium[39, 47-49] or potassium intake.[50-51] The expression of 4A and 4F enzymes differs in males and females.[5, 27, 39] However, the significance of this observation in determining sex differences in the development of hypertension remains to be determined. 20-HETE is metabolized by β-oxidation to shorter chain-length products[52-55] that are less active. It also can be metabolized by COX enzymes to form vasoconstrictor endoperoxides or vasodilator prostanoids.[53, 56-57]

20-HETE in the control of vascular tone

Considerable evidence indicates that 20-HETE plays a critical role in regulation of vascular tone.[52] Renal, cerebral, cardiac and mesenteric arteries all produce 20-HETE and it is a potent vasoconstrictor ($EC_{50} < 10^{-8}$ M).[22, 58-59] 20-HETE activates PKC,[60-63] MAPK,[41, 64-65] src-type tyrosine kinase[63] and rho kinase[66] pathways which all contribute to the regulation of vascular tone. Moreover, 20-HETE phosphorylates and blocks K_{Ca} channel activity[23, 59-60, 63] thereby allowing for sustained depolarization of VSM and Ca^{2+} entry through L-type Ca^{2+} channels. 20-HETE also increases the conductance of L-type Ca^{2+} channels through activation of PKC.[67] More recently, 20-HETE has been reported to enhance the activation of inward nonselective cation currents through transient receptor potential canonical 6 (TRPC6) channels,[68] which are implicated in the myogenic response.[69]

Several lines of evidence suggest that 20-HETE plays a key role in the myogenic response following elevations in transmural pressure. Elevations in transmural pressure increase 20-HETE levels in isolated arterioles[17] and inhibitors of the formation or actions of 20-HETE block the myogenic response of renal and cerebral arterioles *in vitro*[17, 70] and autoregulation of renal and cerebral blood flow *in vivo*.[17, 71] The formation of 20-HETE in vascular tissue is stimulated by angiotensin II (AngII)[21, 72-73], endothelin[73-74], and serotonin (5-HT).[75] Blockade of the formation of 20-HETE attenuates the vasoconstrictor response to these agonists by about 50%.[21, 72-73, 76-79] The production of 20-HETE in renal and cerebral arteries is inhibited by nitric oxide (NO),[23, 80-83] carbon monoxide (CO)[84-85] and superoxide radicals,[86] and the fall in 20-HETE levels partially mediates the cGMP-independent effects of NO on K_{Ca} channels and vascular tone.[23, 80-82, 87] Several recent studies have demonstrated that upregulation of the production of 20-HETE can increase vascular oxidative stress and produce

endothelial dysfunction by activating nuclear factor-kappaβ (NF-kappaβ) which leads to eNOS uncoupling decreased production and availability of NO.[88-90]

20-HETE also participates as a modulator of the tubuloglomerular feedback (TGF) response in the kidney. Perfusion of the loop of Henle with AA potentiates, while CYP inhibitors block the TGF response.[91] Inhibitors to the formation of 20-HETE attenuate the renal vasoconstrictor response to ATP,[92] one of the putative mediators of TGF. The concept that 20-HETE serves as a modulator of TGF is also consistent with previous findings that NO blocks the production of 20-HETE and attenuates TGF; whereas, AngII stimulates the production of 20-HETE and potentiates TGF.

20-HETE and Na^+ transport

20-HETE inhibits sodium transport and Na^+-K^+-ATPase activity in the proximal tubule[93] by activating PKC to phosphorylate the serine23 residue in the alpha subunit of this enzyme.[61, 94-96] Other studies have shown that the inhibitory effects of parathyroid (PTH),[94, 96-98] dopamine,[61] endothelin,[99] and AngII[100-101] on Na-KATPase activity and Na^+ transport in the proximal tubule are dependent on the formation 20-HETE. 20-HETE is also produced and inhibits Na^+-K^+-$2Cl^-$ transport in the thick ascending loop of Henle (TALH).[8-10, 102] This is due in part to an ouabain-like effect of 20-HETE to inhibit Na^+-K^+-ATPase activity in this portion of the nephron.[9, 103] 20-HETE also blocks a 70 pS K^+ channel in the apical membrane of the TALH cells.[51] Blockade of this channel limits K^+ availability for transport via the Na-K-$2Cl^-$transporter and reduces the lumen positive transepithelial potential that serves as the main driving force for the passive reabsorption of Na^+ in the TALH. Previous findings that CYP4A inhibitors increase, while 20-HETE decreases transepithelial potential and Cl^- transport in the TALH[10] further supports this view. Others have reported that the inhibitory effects of AngII,[104-105] bradykinin[106] and elevations in intracellular Ca^{2+} [107-109] on Na^+ transport in the TALH are dependent on the formation of 20-HETE. The inhibitory effects of NO[110] and CO[111] on K^+ channel activity and Na^+ transport in the TALH also appear to be dependent on blockade of the formation of 20-HETE.

Evidence that 20-HETE participates in the pressure-natriuretic response

The concept that the kidney plays a dominant role in the long-term control of arterial pressure is based on the pressure-natriuresis phenomenon.[112] According to this hypothesis, hypertension can only develop if pressure-natriuresis is impaired. The pressure-natriuresis relationship is shifted to higher pressures in every genetic and experimental model of hypertension that has been studied to date.[112] Previous work revealed that pressure-natriuresis is associated with elevations renal medullary blood flow[113-115] and renal interstitial hydrostatic pressure (RIHP)[116-120] and inhibition of Na^+ transport in the proximal tubule.[121-123] More recent studies have demonstrated that elevations in renal perfusion pressure (RPP) are associated with a fall in Na^+-K^+-ATPase activity and internalization of Na^+ transporters from the brush border of the proximal tubule.[124-127] Given the evidence 20-HETE is produced and inhibits Na^+ transport in the proximal tubule and TALH,[5, 7, 9-10, 93-94, 102] the role of this compound in mediating pressure-natriuresis has recently been examined. Elevations in RPP increase the concentration of 20-HETE in the renal cortex secondary to elevations in RIHP and inhibitors of the synthesis of 20-HETE prevent the fall in Na^+-K^+-ATPase activity, the internalization of sodium hydrogen exchanger 3 (NHE3) protein in the proximal tubule and blunt the pressure-natriuretic response of rats by 50%.[117, 128]

Renoprotective actions of 20-HETE

Glomerular capillary pressure (Pgc) is elevated in Dahl S rats[47] and this is associated with upregulation of the glomerular production of transforming growth factor (TGF-β)[129] and

increased permeability of the glomerulus to albumin (Palb)[130] Chronic treatment of Dahl S rats with a TGF-β antibody attenuates the development of proteinuria and renal disease.[129-130] TGF-β was recently found to directly increases Palb is isolated glomeruli and inhibit the formation of 20-HETE. Moreover, administration of 20-HETE prevented the effects of TGF-β on Palb.[130] In further studies, isolated glomeruli were shown to produce 20-HETE and that blockade of the formation of 20-HETE increased Palb.[131] These findings indicate that 20-HETE produced in the glomerulus plays a critical role in maintaining glomerular filtration barrier to albumin and that upregulation of TGF-β in hypertension may initiate the development of proteinuria and renal disease in part by inhibiting the formation of 20-HETE.

Evidence that a deficiency in the renal formation of 20-HETE contributes to the development of salt-sensitive hypertension

Dahl S rats

The Dahl salt-sensitive (S) rat rapidly develops severe hypertension and renal injury when challenged with a high salt diet. Previous studies have indicated that the pressure-natriuresis relationship is shifted toward higher pressures in Dahl S rats[48, 113, 132-133] and that this is associated with an elevation in Cl^- transport in the TALH.[10, 102, 134-136] Given the importance of 20-HETE in the regulation of Na^+-K^+-2Cl^- transport in this portion of the nephron, several studies have examined whether a deficiency in the renal production of 20-HETE contributes to the elevation in loop Cl^- transport and the development of hypertension in S rats. To date nine lines of evidence have emerged that support this hypothesis. 1. The expression of CYP4A protein and the formation of 20-HETE are reduced in the kidney of Dahl S rats.[10, 39, 43, 47-48, 137] 2. The deficiency in the formation of 20-HETE in TALH appears to contributes to elevated loop Cl^- reabsorption in Dahl S rats since exogenous administration of 20-HETE normalizes loop Cl- transport in S rats with having any effect in normotensive control animals in which 20-HETE synthesis is unaltered.[10, 102] In addition, inhibitors of the formation of 20-HETE increase Cl^- transport in normotensive rats but have no effect in Dahl S rats.[10, 102] 3. 20-HETE plays a critical role in modulating TGF[91] and TGF responses and the regulation of Pgc are impaired in SS rats.[47] 4. CYP4A genotype co-segregates with the development of hypertension in an F_2 cross of Dahl S and Lewis rats.[43] 5. Induction of the renal formation of 20-HETE with fibrates lowers blood pressure[138] and normalizes pressure-natriuresis in S rats.[132] 6. Chronic blockade of the formation of 20-HETE blunts the pressure natriuretic relationship and promotes the development salt-sensitive hypertension in salt-resistant strains of rats but it has no additional effect in Dahl S rats[48, 117, 128, 139] 7. Chronic treatment of Dahl S rats with the SOD mimetic, Tempol, increases renal production of 20-HETE, and inhibitors of the formation of 20-HETE block the antihypertensive actions of Tempol.[86] 8. Transferring CYP4A alleles from Lewis rats into the Dahl S genetic background increases the renal formation of 20-HETE, improves pressure-natriuresis and attenuates the development of hypertension.[47-48] 9. Chronic inhibition of the formation of 20-HETE formation rescues the "hypertensive phenotype" in the CYP4A$^+$ congenic Dahl S rats.[47-48] These studies all support the view that a genetic deficiency in the CYP4A enzymes responsible for the formation of 20-HETE contributes to the development of hypertension in Dahl S rats.

Human studies

In the last 5 years, many studies have reported that sequence variants in the CYP4A11 and CYP4F2 genes that produce 20-HETE are linked with the development of hypertension and/or cardiovascular disease in human population studies.[140-156] In this regard, a T to C substitution at nucleotide 8590 resulting in a phenylalanine to serine substitution at amino acid 434 has been identified in the CYP4A11 isoform that decreases the formation of 20-HETE and is associated with increased risk of hypertension in human association studies.[140-141, 147] This

same T8590C polymorphism has also been associated with an increased incidence of hypertension in a cohort of patients with myocardial infarction in Germany.[142-143]

More recently, Stec *et al.* identified a V433M variant in the CYP4F2 isoform that also decreases the formation of 20-HETE.[157] This variant has since been linked with an increased incidence of hypertension,[148, 151] and stroke[145, 153,150] in human population studies. However, more work is needed to determine cause and effect relationships because at least in the hypertension studies the urinary excretion of 20-HETE increased rather than decreased in the hypertensive patients carrying the supposed inactivating variant.[148, 151] Whether this is due to a compensatory upregulation of another isoform or a hypertension-induced increase in the excretion of 20-HETE remains to be explored.

In other studies, a G421C SNP in the CYP4F2 has been associated with hypertension in a Chinese population.[151-152] A haplotype based case control study from Japan that looked at 5 different SNPs in CYP4F2 found that a CC genotype of rs1558139 was a genetic marker for hypertension, while another haplotype was protective.[149]

Role for 20-HETE in other models of hypertension

Spontaneously Hypertensive Rats (SHR)

Iwai et al. first reported that the CYP4A2 gene was overexpressed in the kidney of SHR.[158] Numerous investigators have since found that the production of 20-HETE is elevated in the kidney of the SHR[7, 36-37, 42, 159-160] and that inhibition of the synthesis of 20-HETE lowers blood pressure in this model.[161-164] It was difficult to understand however, why inhibition of the renal production of 20-HETE would lower blood pressure in SHR since 20-HETE inhibits Na^+ transport and would be expected to oppose the development of hypertension. The issue is further clouded by the findings of Sharta *et al*. [165] showing that induction of the renal formation of 20-HETE with fibrates attenuates, rather than promotes, the development of hypertension in stroke-prone SHR. More recent studies have found that vascular production of 20-HETE is elevated in SHR[166] and that enhanced vascular production of 20-HETE contributes to oxidative stress, endothelial dysfunction and enhanced vascular reactivity to pressor hormones, all of which contributes to the elevation in peripheral vascular resistant and the maintenance of hypertension in the SHR.[166-167]

Angiotensin II and Doca salt hypertension

AngII increases the synthesis and release of 20-HETE from rat and rabbit kidneys[100-101] and inhibitors of the synthesis of 20 HETE attenuates the vasoconstrictor actions AngII both in vitro and vivo.[76] Similarly, the production of 20-HETE is elevated in the kidney of AngII-hypertensive rats and blocking the formation of 20-HETE lowers blood pressure in this model. [76] Inhibitors of the formation of 20-HETE also lowers blood pressure in DOCA-salt hypertensive rats.[168] These results suggest that like the SHR, an elevated production of 20-HETE may contribute to the increase in vascular tone and the development of hypertension in these experimental models of hypertension. On the other hand, *Honeck et al*. reported that the production of 20-HETE is reduced rather than elevated in the kidney of DOCA-salt hypertensive mice and that induction of the renal formation of 20-HETE with fibrates can prevent the development of hypertension in this model.[35]

Androgen-induced Hypertension

Androgens increase the expression of CYP4A8 and CYP4A12 in rats and mice, respectively. [34, 44] Recent studies have indicated that administration of the androgen, dihydrotestosterone (DHT), increases arterial pressure and that this is associated with the induction of vascular CYP4A protein and increased formation of 20-HETE, oxidative stress and endothelial

dysfunction.[45] Treatment with an inhibitor of the synthesis of 20-HETE, attenuated the increase in arterial pressure, lowered oxidative stress and corrected endothelial dysfunction.[45] These findings indicate that elevations in vascular 20-HETE production play a critical role in the development of androgen-induced hypertension.

Mouse models

Knockout of the CYP4A14 gene increases blood pressure in male mice.[34, 169] This observation would be consistent with the view that a deficiency in the renal formation of 20-HETE promotes the development of salt-sensitive forms of hypertension. However, CYP4A14 does not produce 20-HETE when incubated with arachidonic acid. Moreover, knockout of this gene increased rather than decreased the production of 20-HETE in the kidney. The authors suggested that the development of hypertension was due to an upregulation of the expression of the CYP4A12 enzyme in the kidney.[34] They suggested that the hypertension may be secondary to renal vasoconstriction.[34] This conclusion, however, remains to be confirmed in the absence of data indicating that blockade of the production of 20-HETE (pharmacological rescue) increases RBF and GFR and lowers blood pressure in this model.

Disruption of the murine CYP4A10 gene has been reported to produce salt-sensitive hypertension.[170] However, much like the CYP4A14 knockout, knockout of the CYP4A10 gene did not reduce the renal formation of 20-HETE.[170] Rather the hypertensive phenotype was associated with a reduction in the renal synthesis of epoxyeicosatrienoic acids (EETs) and enhanced ENaC activity in the collecting duct (CD).[170] Treatment with amiloride, an inhibitor of ENaC, normalizes the blood pressure in CYP4A10 knockout mice.[170] These results suggest that the development of salt-sensitive hypertension in CYP4A10 mice is not due to changes in the renal production of 20-HETE but is associated with inhibition of the renal production of EETs through some unknown mechanism.

Recently, *Liu et al.* reported that overexpression of human CYP4F2 in the proximal tubule of a transgenic mouse model increased the renal formation of 20-HETE and arterial pressure.[171] These authors concluded that the increased renal levels of 20-HETE might contribute to the development of hypertension in this model by increasing renal vascular tone. However, additional experiments showing that inhibitors of 20-HETE increase RBF and GFR and reduce arterial pressure in this model are needed to support this conclusion.

20-HETE agonists and inhibitors in hypertension

Given the overwhelming evidence that the renal and/or vascular production is altered in animal models of hypertension and that mutations in CYP4A11 and 4F2 enzymes are linked to the development of hypertension in human population studies, there is now considerable interest in developing drugs that target the 20-HETE pathway for the treatment of hypertension. A number of selective inhibitors that inhibit the synthesis of 20-HETE have been developed (Figure 1). These include 17-octadecynoic acid (17-ODYA), N-methylsulfonyl-12,12-dibromododec-11-enamide (DDMS), dibromododec-11-enoic acid (DDBB), *N*-hydroxy-*N'*-(4-butyl-2methylphenyl)formamidine (HET0016) and *N*-(3-Chloro-4-morpholin-4-yl) Phenyl-*N'*-hydroxyimido formamide (TS011). More recently, stable analogs 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid (6-,15-,20-HEDE) and 20-hydroxyeicosa-6(Z),15(Z)-dienoyl]glycine (6-,15-,20-HEDGE) that block the vasoconstrictor actions of 20-HETE have also been described.[172-174]

In the vasculature, 20-HETE is potent vasoconstrictor that promotes hypertension. The inhibitors of the synthesis of 20-HETE have been shown to reduce arterial pressure in AngII, DOCA-salt and androgen induced models of hypertension as well as the SHR that all are associated with increased vascular production of 20-HETE, oxidative stress and endothelial

dysfunction. More recently, HET0016, an inhibitor of the synthesis of 20-HETE, was found to also attenuate the development of hypertension and vascular oxidative stress in DHT infused animals.[45] 20-HETE inhibitors and antagonists also reduce infarct size following ischemia and reperfusion of the coronary and cerebral circulations.[19, 166, 175-176] Thus, the use of inhibitors of the synthesis of 20-HETE (17-ODYA, HET0016 and TS011) or 20-HETE antagonists (6-, 15-,20-HEDE and HEDGE) might be prone to be useful to treat hypertension in patients with elevated vascular production of 20-HETE.

At the level of renal tubules, 20-HETE inhibits Na^+ transport and deficiencies in the renal formation of 20-HETE have been reported to promote salt-sensitive hypertension in the Dahl S rat[47-48, 132, 138] and in patients with inactivating mutations in CYP4A11 and 4F2.[140-141, 147, 157] Treatment with the 20-HETE mimetics, 20-hydroxyeicosa-5(Z),14(Z)-dienoic acid (5-, 14-,20-HEDE), *N*-[20-hydroxyeicosa-5(Z),14(Z)-dienoyl]glycine (5-,14-,20-HEDGE), (Figure 1) and PPAR-α agonists (fibrates) or gene therapy to upregulate the renal formation of 20-HETE would be expected to promote sodium excretion and oppose the development of salt-sensitive hypertension. This therapy may also slow the progression of glomerular disease and renal fibrosis since 20-HETE has a protective effect on the glomerular permeability barrier.[130-131] Increasing the renal formation of 20-HETE may also be beneficial for patients following ischemia reperfusion (I/R) injury since recent studies have shown that administration of stable 20-HETE analogues mitigates acute I/R injury via an effect that is likely due to 20-HETE's natriuretic effects.[177] Clearly, further studies are needed to better understand the role of the pro- and antihypertensive actions of 20-HETE in various models, but the available evidence support the view that both 20-HETE agonists/mimetics and antagonists/inhibitors may be new and useful therapeutic targets for the treatment of hypertension and associated cardiovascular complications.

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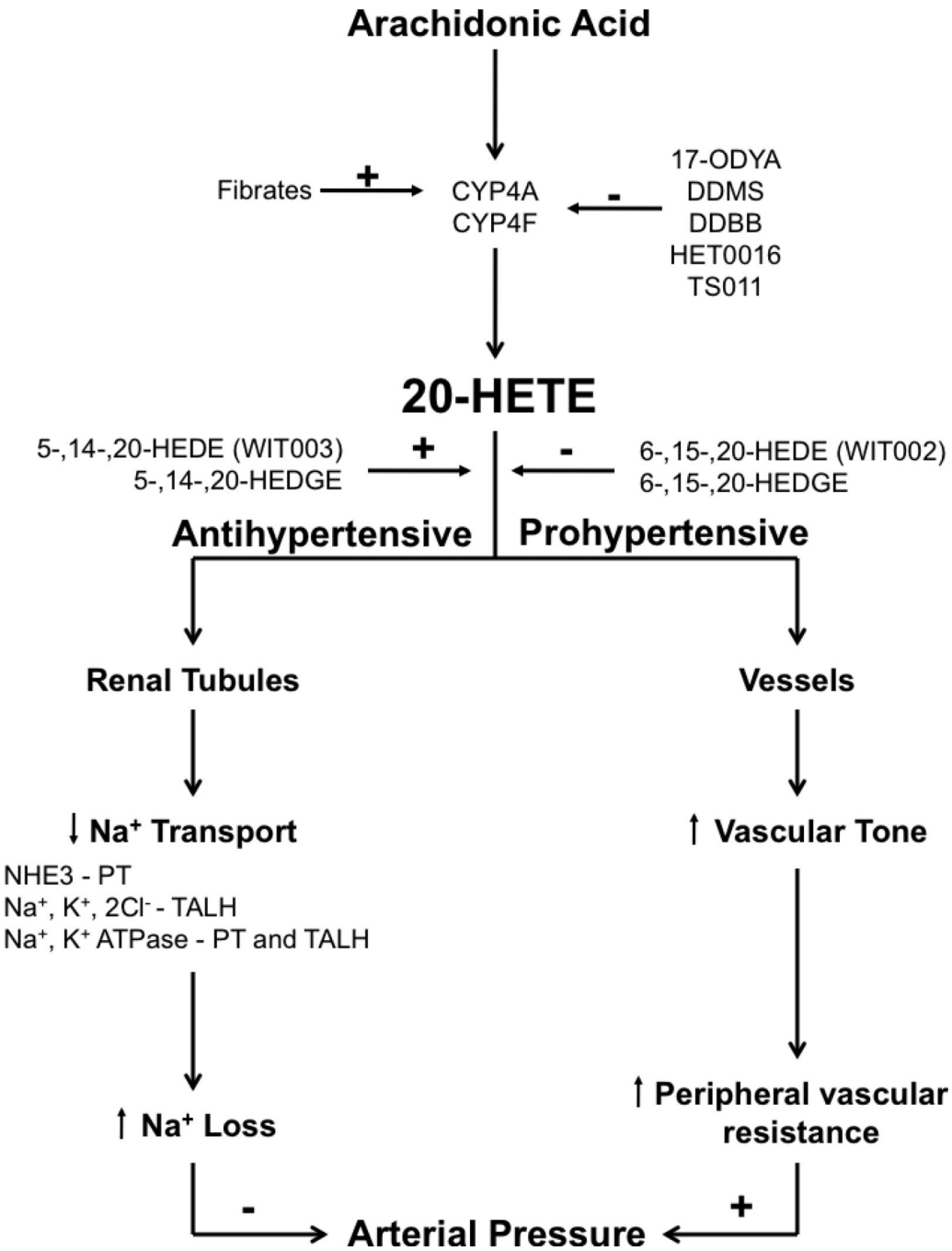

Figure 1. Modulation of the 20-HETE pathway in the control of arterial pressure

Summary of various compounds available to induce or inhibit the actions of 20-HETE on renal tubular transport and/or vascular tone to lower arterial pressure in various models of hypertension. Abbreviations: 20-hydroxyeicosa-5(Z),14(Z)-dienoic acid (5-,14-,20-HEDE), *N*-[20-hydroxyeicosa-5(Z),14(Z)-dienoyl]glycine (5-,14-,20-HEDGE), 20-hydroxyeicosa-6 (Z),15(Z)-dienoic acid (6-,15-,20-HEDE), 17-octadecynoic acid (17-ODYA), N-methylsulfonyl-12,12-dibromododec-11-enamide (DDMS), dibromododec-11-enoic acid (DDBB), *N*-hydroxy-*N*'-(4-butyl-2methylphenyl)formamidine (HET0016), *N*-(3-Chloro-4-morpholin-4-yl)Phenyl-*N*'-hydroxyimido formamide (TS011), sodium hydrogen exchanger 3 (NHE3), sodium, potassium, 2 chloride (Na^+,K^+,$2Cl^-$) cotransporter, sodium potassium

ATPase pump (Na^+,K^+,ATPase), potassium activated calcium (K_{Ca}) channels, proximal tubule (PT), thick ascending loop of Henle (TALH)