Roles of Lipid Mediators in Kidney Injury

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Summary: Small lipids such as eicosanoids exert diverse and complex functions. In addition to their role in regulating normal kidney function, these lipids also play important roles in the pathogenesis of kidney diseases. Increased glomerular cyclooxygenase (COX)1 or COX2 expression has been reported in patients with nephritis and in animal models of nephritis. COX inhibitors have shown beneficial effects on lupus nephritis and passive Heymann nephritis, but not anti-Thy1.1–induced nephritis. 5-Lipoxygenase–derived leukotrienes are involved in inflammatory glomerular injury. Lipoxygenase product 12-hydroxyeicosatetraenoic acid may mediate angiotensin II and transforming growth factor β-induced mesangial cell abnormality in diabetic nephropathy. P450 arachidonic acid mono-oxygenase–derived 20-hydroxyeicosatetraenoic acid and epoxyeicosatrienoic acids are involved in several forms of kidney injury, including renal injury in metabolic syndrome. Ceramide also has been shown to be an important signaling molecule that is involved in the pathogenesis of acute kidney injury caused by ischemia/reperfusion and toxic insults. Those pathways should provide fruitful targets for intervention in the pharmacologic treatment of renal disease.
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An extensive body of evidence shows that small lipids participate as mediators in a variety of transmembrane signaling cascades, mediating multiple cellular processes such as cell differentiation, proliferation, and apoptosis.[1-4] These lipids include eicosanoids, fatty acids, glycerophospholipids, and ceramide.[1-4] In addition to their roles in regulating physiologic function, these lipid mediators also have been shown to play important roles in the pathophysiology of inflammation, asthma, cancer, diabetes, and hypertension,[1-5] pointing to potential therapeutic targets at above-mentioned lipid mediators or the enzyme responsible for their biosynthesis or the receptor mediating their actions. The present review focuses on the current understanding of the roles of arachidonic acid–derived lipid mediators in tissue injury and the repair process in diseased kidney.

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ARACHIDONIC ACID AND PHOSPHOLIPASE A2

Arachidonic acid is a precursor of an array of bioactive lipids, including prostanoids, leukotrienes, and hydroxyeicosatetraenoic acids (HETEs) and epoxyeicosatrienoic acids (EETs), produced through cyclooxygenase (COX), lipoxygenase (LO), and cytochrome P450 monooxygenase (CYP450) pathways, respectively.[2,3,5-7] Collectively, these arachidonic acid–derived lipids are called *eicosanoids* (eicosa, Greek for 20, referring to 20 carbon fatty acids).

Cellular levels of free arachidonic acid available for eicosanoid production are controlled primarily by phospholipase A2 (PLA2).[8] Thus far, more than 20 PLA2s have been identified, which have been classified into 4 groups: secretory PLA2 (sPLA2), cytosolic PLA2 (cPLA2), calcium-independent PLA2, and platelet-activating factor (PAF) acetylhydrolases.[8,9] Six members of the cPLA2 family have been identified: cPLA2α, β, δ, ϵ, ζ, and γ.[10] Among them, cPLA2α (IVA PLA2) is best characterized and is suggested to be a key player regulating arachidonic acid release for eicosanoid biosynthe-

sis.[8,9] The activity of cPLA2 is regulated by mitogen-activated protein kinase, protein kinase C, and Ca^{++}-calmodulin–dependent kinase.[11-13] Endothelin, angiotensin II, and vasopressin have been reported to activate cPLA2.[14-20]

In the kidney, studies show that PLA2 activity can be induced by a variety of stimuli, including oxidative stress, complement C5b-9, hypoxia, and mechanical stretch.[21-24] cPLA2 has been shown to enhance H_2O_2-induced cytotoxicity in kidney epithelial cells and mesangial cells.[25,26] cPLA2 and its products have been shown to participate in several pathogenic processes, including diabetic nephropathy, anti-Thy1 glomerulonephritis, and ischemic kidney injury.[8,10] Recently, considerable evidence has suggested that secretary PLA2s, particularly sPLA2 IIa, sPLA2 V, and sPLA2 X, are involved in atherosclerotic lesions.[27-29] The role of these sPLA2s in the kidney remain to be defined.

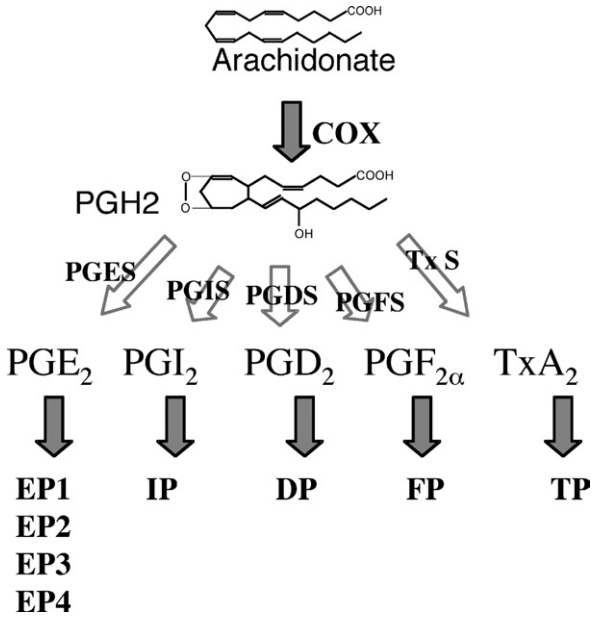

Figure 1. Cyclooxygenase pathway of arachidonic acid metabolism.

COX-DERIVED PROSTANOIDS

Arachidonic acid can be metabolized to prostanoids via the COX pathway. COX first converts free arachidonic acid to prostaglandin (PG)G2 via its *bis*-oxygenase activity, and the unstable PGG2 then is converted to PGH2 by the peroxidase activity of COX.[30] PGH2 subsequently is metabolized to more stable biologically active prostanoids including PGE2, prostacyclin (PGI2), PGF2α, PGD2, and thromboxane A2 (TxA2) by distinct synthases. Each prostanoid acts on specific and distinct cell surface G-protein–coupled receptor(s)[31,32] or on nuclear receptors such as peroxisome proliferator-activated receptor δ and peroxisome proliferator-activated receptor γ (Fig. 1).[33-36]

Prostanoids rapidly are degraded metabolically, limiting their effect to the immediate vicinity of their synthetic site, accounting for their autocrine or paracrine function. The biologic effects of COX-derived prostanoids are diverse and complex, depending on which prostanoid is produced and which receptor is available.[31,32] Thus, the effects of prostanoids on kidney function rely on distinct enzymatic machinery that couples phospholipase and COX to specific prostanoid synthase in specific cells, yielding a specific prostanoid that acts, through autocrine or paracrine, on a specific G-protein–coupled receptor, exerting its distinct effect.[31]

Cyclooxygenases

Two isoforms of COX have been identified, designated COX1 and COX2.[37-40] COX1 appears to serve a constitutive housekeeping role, being responsible for maintaining basic physiologic function such as cytoprotection of the gastric mucosa and control of platelet aggregation.[6,30,41] Conversely, COX2 is induced by inflammatory mediators and mitogens, and is thought to play an important role in pathophysiologic processes including angiogenesis, inflammation, and tumorigenesis.[6,7,30,41] However, recent studies have indicated that COX2 also serves housekeeping functions. Gene-targeting experiments have shown a critical role of COX2 in kidney development, ovulation, and parturition.[42-45] Clinical and animal studies also have shown an important role of COX2 in maintaining cardiovascular homeostasis.[46-48] The expression of these 2 isoforms of COX in the kidney has been documented. COX1 is highly expressed in the collecting duct, and a low level of COX1 also is detected in interstitial cells.[49-51] In contrast, COX2 is expressed predominantly in renal medullary interstitial cells,

in the cortical thick ascending limb, and in cells associated with macula densa under normal conditions.[38,49,52]

Prostanoid Synthases

COX-mediated arachidonate metabolite intermediate PGH2 is catalyzed further by prostanoid synthase. Prostanoid synthases include PGE2 synthase (PGES), prostacyclin synthase (PGIS), PGD synthase (PGDS), PGF synthase, and thromboxane synthase, responsible for PGE2, PGI2, PGD2, PGF2α, and TxA2 biosynthesis, respectively.[41,53] At least 3 PGE synthases have been identified: microsomal PGE synthase 1 (mPGES1), microsomal PGE synthase (mPGES2), and cytosolic PGE synthase.[54-56] mPGES1 displays a high catalytic activity relative to other PGESs.[54,57] The expression of mPGES1 is induced by cytokines and inflammatory stimuli.[54] In contrast, the expression of cytosolic PGES and mPGES2 is not inducible.[56,58] PGD2 is synthesized from PGH2, catalyzed by PGDS.[59] Two distinct types of PGDS have been identified: the lipocalin-type PGDS and the hematopoietic PGDS.[59,60] PGF2α can be synthesized from PGH2 by 9,11 endoperoxide reductase.[61] PGF2α also can be synthesized from PGE2 by PGE 9-ketoreductase.[62,63]

Molecular and/or pharmacologic studies have shown PGES expression or PGE2 biosynthesis in most cell types or tissues involved in immunologic and inflammatory reaction, including the thymus, spleen, dendritic cells, macrophages, eosinophils, neutrophils, and mast cells.[64] PGDS and TxAS expression or activity also has been described in dendritic cells, microphages, eosinophils, neutrophils, and mast cells.[64] In macrophages, PGE2 and TxA2 are major prostanoids, whereas mast cells predominantly generate PGD2.[64] Resting macrophages produce TxA2 in excess of PGE2, this ratio changes to favor PGE2 biosynthesis after inflammatory agent lipopolysaccharide treatment.[64] These studies are consistent with important roles of prostanoids in the regulation of immunologic and inflammatory reactions.

The distribution of prostanoid synthases within the kidney is less well characterized. In the kidney, mPGES1 is expressed in collecting duct and medullary interstitial cells.[65,66] Although mPGES1 has been reported to be functionally coupled to COX2,[58] in renal collecting duct mPGES1 appears to be coupled mainly to COX1.[65] Low levels of mPGES2 and cytosolic PGES also are detected in the kidney.[67,68] Thromboxane synthase is detected mainly in the glomeruli.[66] PGI synthase appears to be localized mainly to vasculature in the kidney.[66] Reverse-transcription polymerase chain reaction showed that lipocalin-type PGDS is expressed strongly in kidney cortex and outer medulla; although hematopoietic PGDS messenger RNA (mRNA) is detected only in microdissected outer medullary collecting duct.[66] PGE2 is the most abundant prostanoid in the kidney, followed by PGI2, PGF2α, and TxA2.[69] Under basal conditions, both COX1 and COX2 pathways are responsible for the biosynthesis of these prostanoids.[69] In contrast, the COX2 pathway contributes to angiotensin II–induced PGE2 and PGI2 generation in the kidney.[69] The cellular sites where these prostanoids are synthesized remain to be defined.

Prostanoid Receptors

A diverse family of membrane-spanning G-protein–coupled prostanoid receptors has been cloned and characterized. These include the D-prostanoid (DP), E-prostanoid (EP), F-prostanoid (FP), I-prostanoid (IP), and T-prostanoid (TP) receptors, each of which selectively reacts with PGD2, PGE2, PGF2α, PGI2, or TXA2, respectively.[31,32] Four subtypes of EP receptors have been identified: EP1, EP2, EP3, and EP4.[31,32] Each prostanoid receptor activates a distinct G-protein–coupled signaling pathway. The IP, DP, EP2, and EP4 receptors are coupled to the stimulatory G protein that signals by increasing intracellular cyclic adenosine monophosphate level, whereas the TP, FP, and EP1 receptors induce calcium mobilization.[31,32] The EP3 receptor is coupled to an inhibitory G protein and reduces cyclic adenosine monophosphate synthesis.[31,32]

The regulation of prostanoid receptors provides additional mechanisms by which COX-derived prostanoids exert diverse actions in physiologic and pathophysiologic processes. All 4 EP receptors have been described in major inflammatory cells including T lymphocytes, B

lymphocytes, macrophages, and mast cells.[64] It has been proposed that activation of different receptors on different cells at different stages of inflammation may account for the proinflammatory or anti-inflammatory action of PGE2.[64,70]

The intrarenal localization of these prostanoid receptors and the consequences of their activation have been characterized only partially.[71] EP1 and EP3 mRNA expression predominates in the collecting duct and thick limb, respectively, where their stimulation reduces NaCl and water absorption, promoting natriuresis and diuresis.[71] The FP receptor is highly expressed in the distal convoluted tubule and collecting duct, where it may exert distinct effects on renal salt transport.[72] Although only low levels of EP2-receptor mRNA are detected in the kidney and its precise intrarenal localization is uncertain, mice with targeted disruption of the EP2 receptor show salt-sensitive hypertension, suggesting that this receptor may play an important role in salt excretion.[73,74] In contrast, EP4-receptor mRNA is expressed predominantly in the glomerulus, where it may contribute to the regulation of glomerular hemodynamics and renin release.[31,75] The IP-receptor mRNA is highly expressed in the afferent arteriole, where it also may dilate renal arterioles and stimulate renin release.[31] Conversely, TP receptors in the glomerulus may counteract the effects of these dilator prostanoids and increase glomerular resistance. At present, there is little evidence for DP-receptor expression in the kidney.[31]

Role of COX-Derived Prostanoids in Inflammatory Renal Injury

The role of COX-derived prostanoids in immunologic and inflammatory disease has been well documented.[30,41] COX2 expression and prostanoid biosynthesis can be induced in macrophage, dendritic cells by such inflammatory agents as lipopolysaccharide, interleukin-1β, and interferon γ.[30,58,76] Prostanoids, particularly PGE2 and PGI2, have been shown to enhance inflammatory reactions,[30,64] and on the other hand prostanoids also have been shown to have anti-inflammatory effects.[70,77] The proinflammatory or anti-inflammatory effects of prostanoids is dependent on the specific prostanoid-receptor subtype, cell population, and context of activation.[70,77]

Increased glomerular COX1 or COX2 expression has been reported in patients with nephritis and in animal models of nephritis.[78-81] Glomerular expression of COX2 is up-regulated in patients with active lupus nephritis and in the lupus nephritis animal model.[78,82] In the murine lupus nephritis model, combined treatment with mycophenolate mofetil and COX2 inhibitor significantly improved survival and reduced renal damage compared with mycophenolate mofetil alone, supporting a role of COX-derived products in the pathogenesis of renal damage in lupus nephritis.[82] COX2 inhibition also has shown a beneficial effect on passive Heymann nephritis, a model of membranous nephropathy.[83,84] Cell culture studies show that thromboxane A2 can be a mediator of complement-induced cytotoxicity of glomerular epithelial cells.[83] In contrast, in an anti-Thy1.1 glomerulonephritis model, an animal model of mesangioproliferative glomerulonephritis that is characterized by endothelial injury, COX2 inhibition is associated with increased mesangiolysis, albuminuria, and delayed recovery from glomerular injury.[85] Further studies have suggested that healing of injured glomerular capillary endothelium in this model may depend on COX2-derived prostanoids; COX2 inhibition may lead to impaired capillary endothelium healing.[85] Further studies are required to define the precise roles of prostanoids in different forms of glomerulonephritis.

Renal COX-Derived Prostanoids and Diabetic Nephropathy

Diabetic nephropathy is characterized by microalbuminuria, glomerular hypertrophy, mesangial expansion with glomerular basement membrane thickening, arteriolar hyalinosis, and global glomerular sclerosis, which ultimately leads to progression to proteinuria and renal failure.[86,87] Increased glomerular filtration rate (hyperfiltration) typifies the early stages of diabetic nephropathy.[86,87] Animal studies show that in streptozotocin (STZ)-induced type I diabetic rats, renal PGE2, PGI2, and TxB2 increase.[88,89] COX2 expression also is increased in the thick ascending limb and macula densa in both type I STZ diabetic and type II diabetic Zucker rats.[90-93] Enhanced macula densa COX2 expression also has been reported in human diabetic kidneys.[94] Selective COX2 inhibi-

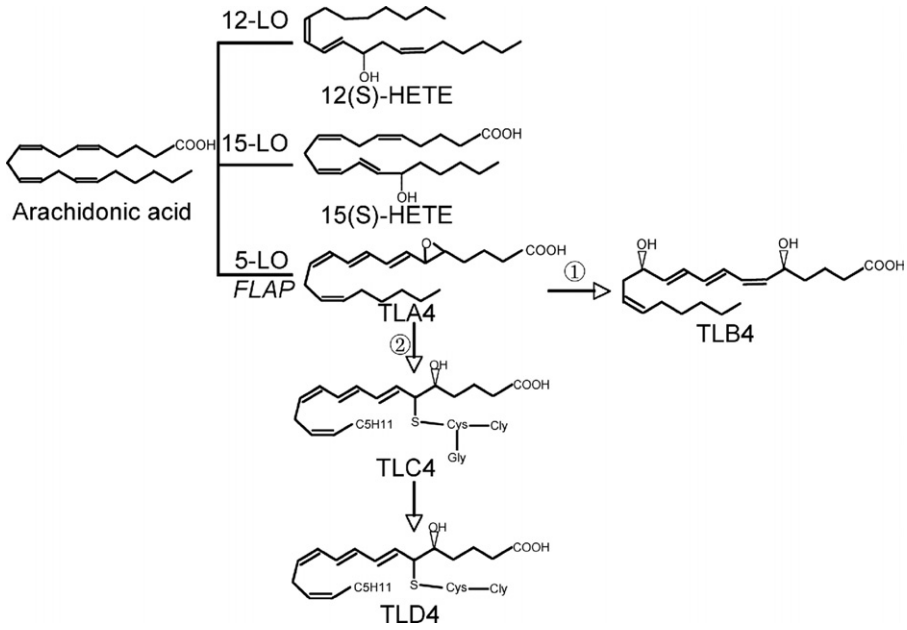

Figure 2. Lypoxygenase pathway of arachidonic acid metabolism. ① Leukotriene A4 hydrolase; ② leukotriene C4 synthase.

tion significantly reduces glomerular hyperfiltration in STZ-induced diabetic rats, consistent with the role of COX2-derived prostanoids in increased renal blood flow in the diabetic kidney.[90] The identity of these prostanoids and their cognate receptors involved in the pathogenesis of diabetic nephropathy has not been characterized completely. Available data have shown that EP1- and EP3-receptor mRNA expression increases in the kidney of STZ-induced and genetic (Akita) type I diabetic mice.[95] EP1-receptor antagonist treatment ameliorates renal and glomerular hypertrophy, and decreases mesangial expansion.[96] Thromboxane receptor (TP) antagonist also has been reported to attenuate proteinuria and ameliorated histologic changes of diabetic nephropathy in diabetic apolipoprotein E–deficient mice.[97] The role of COX-derived prostanoids in the pathogenesis of diabetic nephropathy remains to be explored further.

Renal COX-Derived Prostanoids and Glomerulosclerosis in Chronic Kidney Disease

Several studies have suggested that COX-derived prostanoids also may modify renal function and glomerular damage in chronic renal failure.[98-101] After subtotal renal ablation, renal cortical COX2 expression is increased.[100,101] This increased COX2 expression is most prominent in the macula densa and surrounding cortical thick ascending limb (cTAL).[100,101] Increased COX2 immunoreactivity in glomerular mesangial cells and podocytes from remnant kidneys also has been reported.[100,101] Selective COX2 inhibition decreases proteinuria and inhibits the development of glomerular sclerosis.[100,101] These studies are consistent with a role of COX2-derived prostanoids in the pathogenesis of structural and functional deterioration of the kidney in chronic kidney disease.

LIPOXYGENASE-DERIVED EICOSANOIDS: 5-, 12-, AND 15-HETES AND LEUKOTRIENES

Arachidonic acid also can be oxidized by lipoxygenases to form HETEs and leukotrienes (Fig. 2).[102,103] LOs are a family of nonheme iron-containing enzymes that insert molecular oxygen into polyunsaturated fatty acids such as arachidonic acid and linoleic acid.[102] At least 6 functional human lipoxygenases have been cloned: 5-lipoxygenase (gene name: *ALOX5*), platelet-type 12-lipoxygenase (gene name: *ALOX12*), 12/15-lipoxygenase (leukocyte-type 12-LO for mice, 15-LO type 1 for human, gene name: *ALOX15*), epidermal-type 12-lipoxygen-

ase (gene name: *ALOXE3*), 12(R)-lipoxygenase (gene name: *ALOX12B*), and 15-lipoxygenase type 2 (8-lipoxygenase in mice, gene name: *ALOX15B*).[103]

5-lipoxygenase is the key enzyme in leukotriene biosynthesis.[103] 5-lipoxygenase catalyzes the generation of leukotriene A4 (LTA4) in the presence of 5-LO–activating protein (FLAP). LTA4, in turn, is converted by LTA4 hydrolase to LTB4, capable of activating LTB4 receptors. LTA4 also can be converted to cysteinyl leukotrienes (LTC4, LTD4, and LTE4) through leukotriene C4 synthase.[102] LTC4 and LTD4 contract vascular smooth muscle cells and increase vascular permeability.[104-106] LTB4 is a potent chemotactic substance and increases polymorphonuclear leukocytes (PMN) aggregation and adhesion to the endothelium.[106] These leukotrienes usually are released locally, primarily by leukocytes. These properties of leukotrienes are consistent with their role in mediating inflammatory and allergic reactions.[107-110] Mice with 5-LO gene disruption show a reduced inflammatory reaction, supporting the proinflammatory action of 5-LO–derived metabolites.[103,111]

12-LO catalyzes the formation of oxidized lipids (12[S]-HETE). Human 15-LO type 1 shares high homolog with rodent leukocyte-type 12-LO; both can mediate the formation of 12(S)-HETE and 15(S)-HETE from arachidonic acid, and thus are classified as 12/15-LO.[102,103,112] The production of 12(s)-HETE and 15(s)-HETE has been detected in vascular smooth muscle cells, endothelial cells, monocytes, and platelets.[113-116] Substantial evidence suggests that these eicosanoids play an important role in systemic homeostasis and renal-cardiovascular pathology.[113-116] Recent studies have indicated that 12/15-lipoxygenase products also are involved in the pathogenesis of atherosclerosis. 12/15-lipoxygenase gene deletion is associated with reduced atherosclerosis in animal models.[117-120]

Role of Lipoxygenase-Derived Products in Glomerular Injury

5-LO–derived products have been documented to play an important role in mediating glomerular immune injury.[121,122] 5-LO mRNA and 5-LOX-activating protein (FLAP) mRNA are detected in the glomeruli and vasa recta.[123] Both leukotriene-receptor B4 and the cysteinyl leukotriene–receptor type 1 are expressed selectively in the glomerulus.[123] These studies suggest that 5-LO products are involved in the regulation of glomerular function. Glomerular synthesis of LTB4 and LTC4/LTD4 is enhanced markedly in the early course of several forms of glomerular immune injury, including nephrotoxic serum nephritis, anti-Thy1 nephritis, cationic bovine gamma globulin–induced glomerular injury, and passive Heymann nephritis.[121] LTD4 plays an important role in the reduction of the glomerular filtration rate in the acute phase of the injury by virtue of its potent vasoconstrictor action and contraction of mesangial cells.[121,124] LTD4 also has been reported to increase intraglomerular pressure, which may be associated with proteinuria.[125] A FLAP antagonist has been shown to reduce proteinuria in patients with glomerulonephritis, supporting a role of leukotrienes in proteinuria.[121] LTB4, a potent promoter of PMN attraction, participates in glomerular damage by amplifying PMN-dependent mechanisms of injury.[124]

Role of LO-Derived Metabolites in the Pathogenesis of Diabetic Nephropathy

Accumulating evidence indicates that LO-derived products contribute to the pathogenesis of diabetic complications including diabetic nephropathies.[112] 12/15-LO is detected in renal microvessels, glomeruli, and mesangial cells.[126-128] 12/15-LO levels are increased in the glomeruli of experimental diabetic animals.[128-130] High glucose levels have been shown to directly increase 12/15-LO expression in cultured mesangial cells.[129] The 12/15 LO pathway has been shown to be a critical mediator of transforming growth factor $\beta-$ and angiotensin II–induced mesangial cell hypertrophy and extracellular matrix accumulation.[131-133] Angiotensin II and transforming growth factor β treatment significantly increased 12-LO mRNA expression and formation of the 12-LO product 12(S)-HETE in cultured rat mesangial cells.[112] Angiotensin II–induced mesangial cell hypertrophy and extracellular matrix synthesis in cultured rat mesangial cells can be blocked by an LO inhibitor or targeted 12/15 LO gene deletion.[112,131-133]

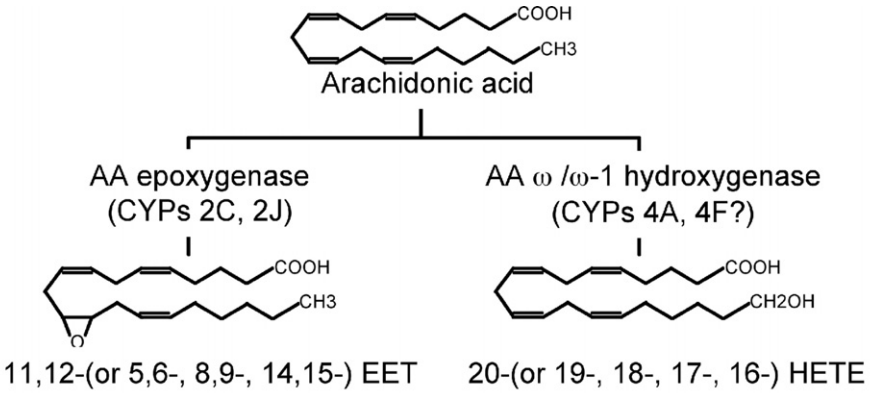

Figure 3. CYP450 monooxygenase pathway of arachidonic acid metabolism.

CYP450 MONOOXYGENASE–DERIVED EICOSANOIDS: 20-HETE AND EETS

Free arachidonic acid also can be oxidized by the cytochrome P450 monooxygenase (CYP 450) to produce hydroxy- and epoxy-arachidonic acid derivatives.[5,134,135] The major CYP450-catalyzed reactions in most tissues are mediated by epoxygenase and ω-hydroxylase activities of the CYP450 family, which are responsible for biosynthesis of EETs and 20-HETE, respectively (Fig. 3).[5,134,135] Molecular biology studies have identified members of the P450 *CYP2C* and *CYP4A* gene subfamilies as functionally relevant epoxygenases and ω-hydroxylases, respectively.[134-137] 20-HETE is a potent vasoconstrictor.[135,138-142] EETs are produced in the vascular endothelium, and are potent vasodilators.[122,134,135,143,144] EETs also are produced in tubules including the proximal tubule and collecting ducts in the rodent kidney.[144,145] EET has been shown to inhibit the amiloride-sensitive epithelial sodium channel (ENaC) activity,[146] which may contribute to their natriuretic effect. EETs also have been shown to mediate the natriuretic effect of angiotensin II.[134,147]

Renal CYP450-Derived Arachidonate Metabolites in Metabolic Syndrome

The metabolic syndrome is a constellation of physical and laboratory abnormalities including hypertension, hyperglycemia, hyperlipidemia, and abdominal obesity.[148] Recent studies indicate that the metabolic syndrome is not only an important risk factor for cardiovascular disease, but also is associated with chronic kidney disease.[149-151] The mechanism underlying this association has not been elucidated completely.[152] Recent studies have shown that in genetic (Zucker rats) and high-fat diet–induced obese animals, renal levels of CYP450-derived eicosanoids are reduced,[92,153] accompanied by reduced CYP2C11 and CYP2C23 protein expression in renal vessels of obese Zucker rats.[92] Reduced CYP450-derived product appears to be associated with renal vascular dysfunction in obese animals. NO-dependent acetylcholine-induced vasodilatation is reduced in obese kidneys.[154] This renal vascular dysfunction in obese rats can be reversed by fenofibrate, a peroxisome proliferator-activated receptor α agonist that increases CYP2C11 and CYP2C23 expression.[154] A high-fat diet that reduces renal EET synthesis also reduces renal sodium excretion, suggesting a potential association between reduced EET production and sodium retention, which may lead to hypertension.[155]

Role of CYP450-Derived Arachidonate Metabolites in Renal Damage

Several studies have shown the role of arachidonate epoxygenase–derived metabolites in renin-angiotensin II–induced kidney damage. Transgenic rats overexpressing human renin and angiotensinogen genes display marked hypertension, and end-organ damage including renal failure and proteinuria.[156,157] The kidneys of these rats show increased infiltration of inflammatory cells and activation of nuclear factor κ B and activating protein-1 (AP1).[158] Renal arachidonate epoxygenase activity and protein levels

of CYP2C11, CYP2C23, and CYP2J are reduced significantly in this animal model.[158-160] Importantly, treatment with fenofibrate increases epoxygenase expression, normalizes blood pressure and albuminuria, reduces nuclear factor κ B activity, and renal leukocyte infiltration in these rats, suggesting that hypertension and renal damage in this rat model is associated with down-regulation of P450 epoxygenase-dependent arachidonic acid metabolism.[158-160]

Increased EET formation has been reported in the kidney of rats with liver cirrhosis.[161] Although it is well documented that renal vasoconstriction leading to impaired renal function occurs during cirrhosis, this result suggests that increased EET synthesis may be a homeostatic response to preserve renal perfusion.[161] Reduced CYP arachidonate hydroxylase activity and 20-HETE levels have been reported in the kidney after ischemia and reperfusion.[162] Reduced CYP4A protein expression and enzyme activity in ischemia/reperfusion is suggested to be an adaptive mechanism to preserve renal vasculature from excessive vasoconstriction.[162]

Recent studies have suggested that CYP hydroxylase–derived product 20-HETE plays an important role in the maintenance of the glomerular protein permeability barrier.[163] An in vitro glomerular albumin permeability study using isolated rat glomeruli shows that puromycin aminonucleoside significantly increases glomerular albumin permeability.[163] 20-HETE treatment blocks puromycin aminonucleoside–induced increase in albumin permeability.[163] Clofibrate that increases CYP4A expression also prevented the isolated glomeruli from puromycin aminonucleoside–induced increases in albumin permeability.[163] This result is consistent with earlier studies showing compounds that reduce proteinuria, such as angiotensin-converting enzyme inhibitor and cyclosporine A, also increase 20-HETE biosynthesis,[164-166] suggesting a potential protective role of CYP hydroxylase–derived products in maintaining glomerular permeability barrier function.

ROLE OF SPHINGOMYELIN AND CERAMIDE IN THE NORMAL AND DISEASED KIDNEY

Ceramide is also an important signaling molecule, playing an important role in cellular responses to stress, cell growth and differentiation, and apoptosis.[167-169] Ceramide is produced mainly from the hydrolysis of sphingomyelin, catalyzed by sphingomyelinase (Fig. 4).[167,168] Ceramide also can be generated through condensation of sphingosine or sphinganine and fatty acyl—coenzyme (Co)A by ceramide synthase (Fig. 4).[169] The direct targets of ceramide include ceramide-activated protein phosphatase, ceramide-activated protein kinase, and protein kinase Cζ. Ceramide-activated protein phosphatase is related to the PPA2 family of phosphatases, and can be inhibited by okadaic acid.[167] A number of intracellular signaling molecules have been shown to be responsive to cellular ceramide levels, including Raf-1, mitogen-activated protein kinase, arachidonic acid, c-myc, the retinoblastoma gene products, and inhibitory κB (IκB).[168] Ceramide synthesis can be induced by 1,25(OH)2 VitD3, tumor necrosis factor α, endotoxin, interferon γ, interleukin-1, retinoic acid, progesterone, and ionizing irradiation.[167] Numerous stresses that initiate apoptosis have been associated with rapid ceramide generation, including ionizing radiation, heat shock, oxidative stress, daunorubicin, and vincristine, consistent with the critical role of ceramide in apoptosis.[169]

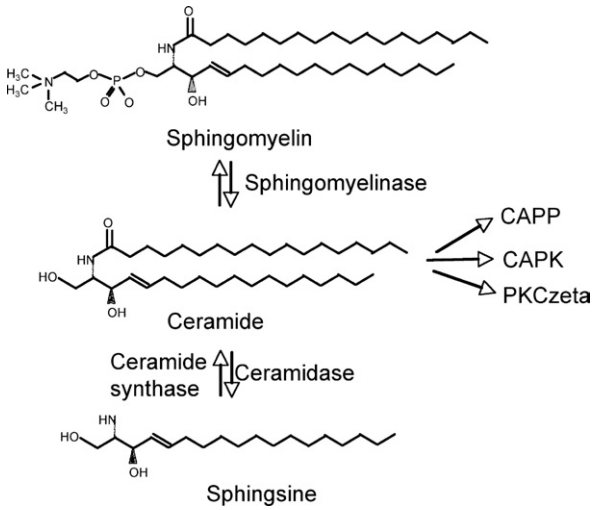

Figure 4. Ceramide biosynthesis.

It has been documented that ceramide is involved in the pathogenesis of acute kidney injury caused by ischemia/reperfusion, toxic insults, and oxidative stress.[170-173] In normal mouse kidney cortex, C24, C22, and C16 cer-

amides have been identified.[174] Ischemia/reperfusion or nephrotoxic injury (glycerol-mediated myohemoglobinuria, radiocontrast) cause a transient reduction of renal ceramide levels, followed by a 2- to 3-fold increase in ceramide levels.[173,175,176] The increased ceramide level after renal injury does not seem to be associated with enhanced hydrolysis of sphingomyelin because sphingomyelinase expression is not increased but rather is reduced throughout the experiments.[172] In contrast, hypoxia-reoxygenation or radiocontrast-induced renal tubular epithelial cell injury is attenuated by the ceramide synthase inhibitor, fumonisin B1, suggesting that increased ceramide synthase activity is responsible for increased ceramide generation, leading to apoptotic change of the renal epithelial cells.[176,177] Of interest, recent studies in mesangial cells show that ceramide mediates enhanced collagen synthesis in response to homocysteine, which has been documented to play an important role in glomerular sclerosis.[178]

SUMMARY

Eicosanoids exert diverse and complex functions. The specific effect of each eicosanoid depends on sequential enzymatic machinery in a specific cell, yielding a specific eicosanoid, exerting its distinct function. The biosynthesis of each eicosanoid is regulated at multiple levels from phospholipase A2, which catalyzes the release of arachidonic acid to specific enzymes that catalyze the formation of bioactive eicosanoids. Arachidonate-derived eicosanoids including prostanoids, leukotrienes, 12/15-HETEs, EETs, and HETEs, and sphingomyelin-derived ceramide, play important roles in maintaining normal renal function. They also are involved in the pathophysiology of diabetic nephropathy, and inflammatory or toxic glomerular injury. Those signaling pathways should provide fruitful targets for intervention in the pharmacologic treatment of renal disease.

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