Emerging roles for eicosanoids in renal diseases

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Purpose of review

Eicosanoids are products of arachidonic acid metabolism which have important roles in renal homeostasis and disease. In recent years the development of genetically modified animals and new drugs targeting eicosanoids producing enzymes and receptors has unveiled new roles for eicosanoids in kidney function. This review provides an overview of eicosanoid biosynthesis and receptors and discusses recent findings on their role in acute and chronic renal diseases and in renal transplantation.

Recent findings

Products of the cyclooxygenases, 5-lipoxygenase, and cytochrome P450 pathways of arachidonic acid metabolism act through distinct receptors presented at different segment of the nephron. Apart from its role in renal physiology and hemodynamic, eicosanoids actively participate in the pathogenesis of acute and chronic renal diseases and have immunoregulatory role in kidney transplantation.

Summary

The new discoveries on the role of eicosanoids in kidney functions and the development of drugs targeting eicosanoids synthesis or action should help to envisage novel therapeutic approaches for patients suffering from renal diseases.

Keywords

acute renal injury, eicosanoids, end-stage renal disease, hypertension, transplantation

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Introduction

Cellular responses are followed by rapid remodeling of membrane phospholipids by activated lipases with concomitant generation of biologically active lipids that can act as mediators of intracellular or extracellular events. Activation of phospholipases is a critical step in the synthesis of these mediators because they cleave membrane phospholipids generating arachidonic acid (AA), an essential fatty acid with 20 carbon atoms and 4 double bonds, which can be bioconverted into eicosanoids via a variety of metabolic pathways. The best known pathways are the cyclooxygenase (COX) which converts AA into prostanoids, the 5-lipoxygenase (5-LO) which converts AA into leukotrienes and the cytochrome p450 (CYP-450) pathway which gives rise to both epoxyeicosatrienoic and 20-hydroxyeicosatetraenoic acid.

Prostanoids are generated via COX or prostaglandin H (PGH) synthase which incorporates molecular oxygen into AA to form PGH_2, which is further metabolized by prostanoid synthases, PGES, PGIS, PGDS, PGFS, and TXS, responsible for PGE_2, PGI_2, PGD, $PGF_{2\alpha}$, and TXA_2 biosynthesis, respectively. Three PGES have been identified: microsomal PGES1 and 2 and cytosolic PGES. The PGES1 is induced by inflammatory cytokines and mediators, whereas mPGES2 and cPGES are constitutively expressed.

Two isoforms of COX are well described, with COX-1 being the constitutive enzyme originally found in bovine prostate. Ferreira *et al.* in 1971 suggested that the mechanism of anti-inflammatory effect of the nonsteroid anti-inflammatory drugs involved inhibition of prostaglandin synthesis [1]. Following the discovery in 1990 of a COX induced by inflammatory stimuli (COX-2), a series of compounds were developed which were more selective for this enzyme. Approximately 60% of the polypeptide sequences of COX-1 and COX-2 are similar, although their regulation is quite different [2]. However, it was later found that COX-2 is expressed constitutively in certain tissues (vascular endothelium, respiratory epithelium, central nervous system) and is thus responsible for prostanoid synthesis for homeostatic functions. A third isoform (COX-3) has been described in rodents with an as yet unknown function.

In humans, there are physiological processes in which each COX isozyme is uniquely involved (e.g. platelet aggregation for COX-1; ovulation, blastocyst implantation, inflammation resolution, perinatal kidney development; and ulcer healing for COX-2) and others in which both

Table 1 Localization and main physiological functions of COX, prostanoid synthases, and receptors throughout the nephron

	Local expression	Physiological function
Cyclooxygenases		
COX-1	Highly expressed in the collecting duct	Cortical and medullary PGE_2 synthesis
COX-2	Medullary interstitial cells, cortical thick ascending limb and macula densa	Synthesis of PGs during stress and kidney development
COX-3	Highly expressed in rodents kidney	Unknown
Synthases		
mPGES1	Highly expressed in the collecting ducts and macula densa	Local synthesis of PGE_2.
mPGES2	Renal cortex	Unknown
cPGES	Epithelial cells	Unknown
L-PGDS	Cortex and outer medulla	Unknown
H-PGDS	Collecting ducts	Unknown
TXS	Glomeruli	Potent vasoconstrictor and increase intracellular Ca^{2+}
PGIS	Mainly associated to renal vasculature and glomeruli	Regulator of renal hemodynamic and a critical mediator of renin release
Prostaglandin receptors		
EP1	Predominates in the inner medulla, collecting ducts	Facilitates angiotensin II mediated vasoconstrictor and inhibits sodium and water reabsorption
EP2	Localization uncertain	Role in salt excretion
EP3	Predominates in the thick ascending limb and deeper collecting ducts	Inhibits renal water and salt absorption
EP4	Predominates in the glomeruli	Regulation of glomerular hemodynamics
DP	Renal expression doubtful	Unknown
FP	Predominates in the superficial collecting ducts	Inhibits renal water absorption
IP	Afferent arteriole and glomeruli	Renal hemodynamics and renin secretion
TP	Glomeruli	Increase glomerular resistance and reduce glomerular filtration rate

isozymes function hand-in-hand (e.g. carcinogenesis and inflammation). In contrast, there are physiological events in which one isozyme can compensate when the other is lacking (e.g. parturition and remodeling of the ductus arteriosus) [3]. In adult human kidney, Komhoff *et al.* [4] found COX-1 in collecting duct cells, interstitial cells, endothelial cells, and smooth muscle cells of preglomerular and postglomerular vessels. Expression of COX-2 protein is constitutive in endothelial and smooth muscle cells of arteries and veins, as well as in podocytes [4]. A more detailed localization of COXs and prostanoid synthases in the kidney are depicted in Table 1.

Prostanoids are rapidly metabolized, essentially in the lungs and liver, by a process that involves active uptake. PGI_2 and TXA_2 are unstable, presenting a half life in physiological pH and temperature of 2–3 min or 30 s, respectively, and are then transformed into the inactive metabolites 6-keto-$PGF_{1\alpha}$ and TXB_2. The biological effects of prostanoids derive from their interaction with specific receptors. Each prostanoid acts on specific G protein-coupled receptors present on the cell surface or on nuclear receptors, such as peroxisome proliferator-activated receptors α, γ, and δ [5–7]. Prostanoid receptors include the D-prostanoid (DP), E-prostanoid (EP), F-prostanoid (FP), I-prostanoid (IP), and T-prostanoid (TP), which react with PGD_2, PGE_2, PGF_{2a}, PGI_2, and TXA_2, respectively [8]. Four subtypes of EP receptors have been cloned: EP1, EP2, EP3, and EP4 [9]. The IP, DP, EP2, and EP4 receptors are coupled to the stimulatory G protein (G_s) and increase cAMP levels, whereas TP, FP, and EP1 receptors induce calcium mobilization in most tissues, whereas the EP3 receptor is coupled to an inhibitory G-protein (G_i) and reduces cAMP synthesis (reviewed in [10] and [11••]). The renal expression of the receptor subset along with its physiologic role is shown in Table 1.

Leukotrienes are derived from the metabolism of AA by the 5-LO enzyme which oxygenates AA at position C-5. This enzyme acts in concert with the 5-LO-activating protein (FLAP), which has no enzymatic activity but enhances the ability of the 5-LO to interact with AA. In resting leukocytes, the 5-LO is located in the cytoplasm or within the nucleus. Upon cell activation the PLA2 and 5-LO enzymes translocate into the nuclear membrane. PLA2 then hydrolyzes the membrane phospholipids generating free AA which binds to the FLAP and in this state becomes sensitive to the action of 5-LO [12]. Unlike the COX enzymes, 5-LO is inactive in resting cells. Upon cell activation, the intermediate LTA_4 is generated and this compound can be hydrolyzed to form LTB_4 or conjugated with glutathione to form cysteinyl-LTs (cysLTs), LTC_4, LTD_4, and LTE_4. Leukotrienes are found within the nucleus, in the cytoplasm, or can be exported from the cell by specific transporter proteins [12]. The discovery that leukotrienes and 5-LO exist within the nucleus is intriguing and raises new questions concerning the role of these mediators in cell function.

Leukotrienes are mainly synthesized by neutrophils, eosinophils, monocytes/macrophages, mast cells, and dendritic cells, but lymphocytes do not synthesize LTs. Other cell types, however, are able to produce leukotrienes by a process termed 'transcellular biosynthesis' in which cells that lack 5-LO can take up leukocyte-derived intermediate LTA_4 and metabolize it into leukotrienes [13]. Leukotrienes act by binding to specific receptors located in the plasma membrane of leukocytes and structural cells. Triggering of leukotriene receptors activates G-proteins and consequently increases intracellular calcium and leads to a reduction in cAMP levels. Two subtypes of LTB_4 receptors have been proposed: the BLT1 is the high-affinity receptor and mediates leukocytes adherence to vascular endothelium, whereas the BLT2 is the low-affinity receptor and mediates leukocytes desgranulation and enzyme release (reviewed in [14]).

Cytochrome P (CYP)-450 products are often referred to as the third pathway of AA metabolism. CYP-450 enzymes are membrane bound and exist as a multienzyme system that acts on several endogenous substrates, including AA, to generate 20-hydroxyeicosatetraenoic acid (20-HETE) and 11,12-epoxyeicosatrienoic acids (EETs). These compounds play critical roles in the regulation of renal, pulmonary, and cardiac function. The 20-HETE is a potent vasoconstrictor implicated in the regulation of muscular tone, whereas the EETs are generally associated to vasodilatation and modulation of angiogenesis and inflammation. These metabolites of AA are important intracellular signaling molecules. Intracellular levels of EETs are tightly regulated; one of the most important EETs/metabolizing enzymes is the soluble epoxide hydrolase. Inhibition of this enzyme would thus be expected so as to increase the intracellular levels of EETs and thus prolong their vasodilator properties. Conversely, overexpression of this enzyme would promote hypertension [15].

The free radical-catalyzed peroxidation of AA, independent of COX enzyme activity, forms a unique series of prostaglandin-like compounds denominated isoprostanes. Although beyond the scope of this review, isoprostanes are markers of oxidative stress and potent vasoconstrictors in various vascular beds, including the kidney [16,17].

Eicosanoids and hypertension

The influence of AA metabolites on control of arterial blood pressure (BP) has been studied for many years [18,19]. The association of kidney COX, 5-LO, and CYP-450 enzymes with renal hemodynamic alterations that could possibly contribute to the development of hypertension has been elucidated in recent decades [19]. COX-2 appears to be involved in maintaining sodium excretion, glomerular filtration, and renal blood flow [20]. There is evidence that COX-2 is responsible for synthesis of dilator PGE_2 and PGI_2, and that COX-1 mediates synthesis of TXA_2 [20]. In the kidney, prostaglandins are important mediators of vascular tone, salt and water balance, and renin release [20].

COX enzymatic products can have antihypertensive and pro-hypertensive properties depending on the profile of prostanoids produced and the model of hypertension. COX inhibitors may actually raise BP and antagonize the effects of antihypertensive medication [20]. Decreased production of prostaglandins may contribute to increased renal vascular resistance in hypertension. The inability of vasodilator prostaglandins to counteract the renal vascular response to angiotensin II appears to contribute to the increased vascular resistance in angiotensin-induced hypertension and in the spontaneously hypertensive rat [21,22]. Qi *et al.* [22] assessed BP response to angiotensin in COX-1-deficient and COX-2-deficient mice and found that COX-2-deficient mice or mice infused with a COX-2 inhibitor had an enhanced response, whereas COX-1-deficient mice had an attenuated BP response to angiotensin. PGI_2 receptor-deficient mice had significantly attenuated rises in BP following induction of two-kidney, one-clip hypertension, which suggests that PGI_2 receptors do not oppose but actually contribute to high BP in renal vascular hypertension [23]. A selective inhibitor of PGI_2, SC-58125, also significantly reduced the increased plasma renin activity and renin mRNA expression in wild-type mice with renal artery stenosis, yet these effects were absent in PGI_2 receptor-deficient mice [23]. When the renin–angiotensin–aldosterone system was activated by salt depletion, SC-58125 blunted the response in wild-type mice but not in PGI_2 receptor-deficient mice.

TXA_2 receptor activation also contributes to the increase in renal vascular resistance and BP in angiotensin-induced hypertension [24]. Studies in TXA_2 receptor-deficient mice have demonstrated that the slow pressure response to angiotensin is attenuated by the lack of this receptor and was partially as a result of a decrease in renal vascular resistance [24,25].

These findings highlighted the varied regulation and actions of COX metabolites and the difficulties in predicting their contribution to renal vascular resistance and BP control.

CYP450-derived epoxygenase metabolites are involved in renal blood flow regulation and long-term arterial BP control by vasodilating the blood vessels and by causing natriuresis [18,19]. Growing evidence suggests that CYP4A synthesis of 20-HETE in the renal vasculature

acts in a pro-hypertensive manner, whereas tubular 20-HETE generation increases sodium excretion and can actually lower BP [18,19]. This increase in renal vascular 20-HETE production was first described in the SHR and exploited the role of 20-HETE in the development of hypertension [18], whereas 20-HETE seems to contribute to the increase in BP by increasing renal vascular resistance. These data demonstrated that inhibition of 20-HETE production decreased renal medullar vascular resistance and BP in the SHR [18,19]. CYP2C-derived EETs are vasodilators and can be converted into inactive diols by the soluble epoxide hydrolase enzyme [26]. Acutely raising EET levels abolished the enhanced afferent arteriolar reactivity to angiotensin in hypertensive rats [27]. Treatment with the peroxisome-proliferator-activated receptor (PPAR)-α activator fenofibrate resulted in increased kidney CYP2C23 expression, lower BP, and protection from renal injury in hypertensive double transgenic rats harboring both the human renin and human angiotensinogen genes [28].

Salt-sensitive, essential, hypertensive patients have an impaired renal natriuretic response to furosemide due to a decreased urinary 20-HETE excretion [29]. A functional variant of a CYP4A hydroxylase, CYP4A11, which encodes for a mono-oxygenase with reduced 20-HETE synthase activity, has a greater prevalence in hypertensive compared with normotensive Caucasians [30].

The incidence of essential hypertension increases with obesity; however, the mechanisms that link obesity with hypertension are not totally clear. Renal CYP450-derived HETEs, EETs, and dihydroxyeicosatrienoic acids (DHETs) have been shown to contribute to renal damage in obesity and diabetes [27,31]. Obese patients with hypertension have decreased urinary 20-HETE excretion, in which this is associated with increased plasma insulin levels [29], which suggests that insulin has an inhibitory effect on CYP4A expression.

Eicosanoids and acute renal injury

The fact that COX inhibition by nonsteroidal anti-inflammatory drugs (NSAID) is linked to acute renal injury since it can cause a severe decrease in glomerular filtration rate (GFR) has long been stated [20]. In the state of normal volemia, prostanoids seem to have little impact on GFR; however, in volume-depleted patients, the maintenance of normal renal function is dependent on prostanoids [20,32–34]. Human and animal studies support the notion that both COX isoforms are important for renal hemodynamics [35–38]. The expression of COX-2 in macula densa is responsible for the PGE_2 and PGI_2 production that maintain GFR by dilating the afferent arteriole mainly through EP4, EP2, and IP signaling [39–41]. AA metabolites are intrinsically related to angiotensin and endothelin-induced renal vascular constriction, a hallmark in acute renal injury [42]. The PGs synthesized from the macula densa can increase renin secretion by converting angiotensin I into angiotensin II that in turn increase intra-glomerular pressure maintaining GFR through constriction of efferent arteriole [43,44].

CYP-450 metabolic pathway and the lipoxigenase-derived lipoxins also contribute to the enhanced renal vascular angiotensin constrictor response in the renal failure model [42]. However, synthetic analogues of lipoxins are beneficial as a treatment for ischemic acute renal injury [45,46]. LXA_4 and aspirin-triggered lipoxins can oppose the LT-mediated renal constrictor and inflammatory responses [45,46]. Controversial data exist on the benefits of inhibition of COX pathway in acute renal injury models. Some investigators have demonstrated that selective and nonselective blockade are associated with renal function improvement through downregulation of inflammatory response and reactive oxygen species (ROS) production, whereas others have found no protection [47,48,49•].

Eicosanoids and chronic kidney disease

Experimental and clinical data highlight the role of eicosanoids in chronic kidney disease (CKD) and as mediators of renal failure progression or as markers of systemic oxidative stress and inflammation. In the rat remnant nephrectomy model, COX-2 is upregulated after renal fibrosis [50], mainly in the macula densa, with a significant negative correlation with renal function. In a rat model of CKD, EP4 (CP-043,305-02) agonist was able to increase GFR and to decrease glomerulosclerosis and tubular atrophy at 9 weeks following therapy [51]. In humans, PGI_2 analogue [52] and combined therapy with ACEI and PGE_1 analogue [53] were able to lessen the progression of CKD.

The 5-LO pathway is activated in peripheral mononuclear blood cells of CKD patients and in those on dialysis therapy [54]. Pro-inflammatory cytokines and reactive oxygen species (ROS) are implicated in this activation and these mediators are closely associated with biocompatibility of the dialysis membrane. Indeed, cuprophane membranes are associated with higher levels of LTB_4 and LTC_4 than polyacrylonitrile varieties [55–57]. Omega 3 supplementation has been associated with decreased oxidative stress and 5-LO expression in these patients [58]. Administration of oil rich in long chain fatty acids was able to decrease LTB_4 while improving clinical symptoms in CKD patients [59]. 5-LO has also been inhibited by vitamin E therapy in hemodialysis patients [60,61].

Hemo and peritoneal dialyses are associated with lipid peroxidation and systemic inflammation. This association

is critically involved in the higher cardiovascular risk observed in these patients compared to healthy controls. Plasma and dialysate levels of isoprostanes are closely associated with these parameters [62–64]. Recently, it has also been demonstrated that 15-F(2t)-isoprostane serum levels are increased in CKD patients and positively associated with advancing stages [65].

Eicosanoids and kidney transplantation

Although there is evidence suggesting a role of various prostanoids in transplantation, the actions of prostaglandin E_2 (PGE_2) and TXA_2 are the most thoroughly characterized to date [66]. Foegh and colleagues [67] described elevated levels of TXA_2 metabolites in the urine of patients with kidney rejection. Subsequently, the same authors and other groups proved the role of TXA_2 in graft rejection using animal models [68–70]. Rocha *et al.* [71] demonstrated that kidney graft survival was prolonged in mice deficient of the TP receptor compared to wild type.

In human settings, the expression of COX-1 and COX-2 isoforms has been demonstrated in renal allografts undergoing acute and chronic allograft nephropathy [72]. Rangel and colleagues [73,74] demonstrated that both isoforms correlated with the severity of acute kidney rejection, namely, there was an increase of COX-2 expression from grade IB to III in vessels, inflammatory infiltrating cells in interstitial areas and in glomeruli, whereas borderline and IA grades had intermediate levels of expression.

However, as PGE_2 tends to inhibit or suppress immune responses, administration of its analogs inhibits rejection and prolongs survival [66]. Analogues to PGE_1, misoprostol and enisoprost, have been studied in cyclosporine-treated renal-transplanted patients with no significant evidence of graft function improvement [75–77].

Even less is known about the role leukotrienes play in kidney transplantation. Inhibition of peptido-LTs has a modest effect on renal function and genetic production of LTB_4 did seem to be required for rejection [78,79]. Besides, CysLTs might also contribute to graft rejection since LTC_4 levels were found to be enhanced in rejecting rat kidneys correlating with the development of cellular infiltrates [79].

Goulet *et al.* [80] demonstrated that 5-LO-deficient mice actually had lower kidney graft survival than fully competent mice. These data provides fresh insight on a possible immunomodulatory role of 5-LO products. Honig and associates [81] found that FTY720, an immunosuppressive drug that promotes T cell homing from spleen and peripheral blood to lymph nodes, induces release of CysLT that ultimately enhances CCL19-induced and CCL21-induced chemotaxis.

The abrogation of blood supply triggers isoprostanes secretion by renal tubular cells and thus contributes to vasoconstriction and graft dysfunction after prolonged cold ischemia times. Indeed, significantly increased plasma F(2)-isoprostane levels have been detected after renal ischemia and reperfusion [16]. Moreover, administration of deferrioxamine, a drug widely used for iron overload treatment as chelating, or propofol, an anesthetic with antioxidant properties, during cold graft storage improved renal function and decreased isoprostane release in a rodent transplant model [82,83]. Isoprostane isoforms are also used as oxidative and inflammatory markers after transplantation [84,85]. They have good correlation with pro-inflammatory cytokines and with acute phase proteins; the levels therefore decrease after transplantation compared to dialysis.

Conclusion

The use of genetically modified animals and of drugs targeting the pathways of eicosanoids synthesis and action has unveiled new roles for these mediators in the pathogenesis of renal diseases. The diversity of enzymes and eicosanoids receptors distributed throughout the kidney highlights the complexity of this system in the normal and pathological conditions. In this sense, in renal disease, it is becoming increasingly clear that eicosanoids might represent a target as well as a therapy in promoting better organ and patient outcomes.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 91).

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