The role of eicosanoids in renal diseases – potential therapeutic possibilities

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Eicosanoids are biologically active molecules that are created in the process of oxidation of arachidonic acid (AA) which is a constituent of the cell membrane phospholipids. Throughout the years it was evidenced by experiments that the lipid and lipid-derived metabolites play an important role in physiological and pathological processes in the kidneys. They are being considered as biomarkers in detecting acute kidney injury, nephrotoxicity, glomerulonephritis and early stages of diabetic nephropathy because of their participation in inflammatory processes and in oxidative stress. They might be also considered as potential novel targets of therapy. However, the role of eicosanoids is still not fully clear and needs to be explored in future studies. In this brief review, studies on the role of eicosanoids in physiological and pathological conditions, e.g. acute kidney injury (AKI) and chronic kidney disease (CKD), and in different renal replacement therapies, including kidney transplantation, are being discussed.

Key words: eicosanoids, acute kidney injury, chronic kidney disease, dialysis, renal transplantation

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Eicosanoids are biologically active molecules that are created in the process of oxidation of arachidonic acid (AA) which is a constituent of the cell membrane phospholipids. Throughout the years it was evidenced by experiments that the lipid and lipid-derived metabolites play an important role in physiological and pathological processes in the kidneys. They are being considered as biomarkers in detecting acute kidney injury, nephrotoxicity, glomerulonephritis and early stages of diabetic nephropathy because of their participation in inflammatory processes and in oxidative stress. They might be also considered as potential novel targets of therapy. However, the role of eicosanoids is still not fully clear and needs to be explored in future studies. In this brief review, studies on the role of eicosanoids in physiological and pathological conditions, e.g. acute kidney injury (AKI) and chronic kidney disease (CKD), and in different renal replacement therapies, including kidney transplantation, are being discussed.

Abstract

Eicosanoids are biologically active molecules generated in the process of oxidation of arachidonic acid (AA) which is a constituent of cell membrane phospholipids. Similarly to AA, the eicosanoid chain is created from 20 carbon atoms. Phospholipase A2 (cPLA2), a cytosolic enzyme, catalyzes the hydrolysis of ester bonds of phospholipids and releases free AA, which is then converted into eicosanoids (Smith & Murphy, 2002). There are three main metabolic pathways involved in the eicosanoid production and catalyzed by the following enzymes: cyclooxygenase (COX), which converts AA to prostanoids (prostaglandins, prostacyclins and thromboxanes), lipoxygenase (LOX) which first converts AA into the hydroperoxyeicosatetraenoic acid (HPETE), and then gives rise to leukotriens, lipoxines and 5-, 12-, 15-hydroxyeicosatetraenoic acid (HETE). And last but not least, AA is converted into epoxyeicosatrienoic acids (EEs) and 20-HETE via the cytochrome P-450 monoxygenase (CYP 450) pathway. AA may also undergo non-enzymatic peroxidation to isoprostanes (Burdan et al., 2006; Câmara et al., 2009; Sałata & Dołęgowska, 2014).

Here, we review the role of eicosanoids in physiological and pathological conditions, e.g. acute kidney injury (AKI) and chronic kidney disease (CKD), and in different renal replacement therapies, including kidney transplantation. Major findings in the experimental and clinical studies on the role of eicosanoids are presented in Table 1. Metabolism of arachidonic acid and potential therapeutic possibilities are shown in Fig. 1.

PHYSIOLOGY OF EICOSANOIDS IN THE KIDNEYS

The COX pathway

Among the prostanoids, the most important biological activity in the kidneys is held by prostaglandin D2 (PGD2), prostaglandin E2 (PGE2) and prostaglandin F2 (PGF2) (Sałata & Dołęgowska, 2014). There are 3 forms of cyclooxygenase described in the literature. COX 1 is a constitutive enzyme that takes part in the maintenance of homeostasis, but it is also expressed in pathological conditions, such as cervical tumors and the Alzheimer’s disease (Sales et al., 2002; Sales & Jabbour, 2003; Hoozemans et al., 2008). There is a high concentration of this enzyme in the renal collecting duct epithelial cells and vascular smooth muscles cells. COX 2 is an induced isof orm of cyclooxygenase and is mainly associated with inflammation. When it comes to kidneys, it is mainly produced in the glomerulus, cells of renal papilla, and especially in the medullary interstitial cells, macula densa and ascending limb of Henle’s loop (Câmpean et al., 2003; Burdan et al., 2006; Sałata & Dołęgowska, 2014; Norregaard et al., 2015). The third isof orm – COX 3 – which is a post-transcriptional modification of COX 1, is selectively inhibited by paracetamol and can act as a regulator in the thermoregulatory center of the brain (Schwab et al., 2003; Câmara et al., 2009). PGE2 is the major prostaglandin expressed in the kidneys. It is produced by 3 isof orms of the prostaglandin E synthase-
two microsomal and one cytosolic synthases. PGE2 regulates the function of kidneys through its four receptors – EP1-4 (Regner, 2012; Nasrallah et al., 2014). They play an important role in inhibiting sodium and water re-absorption, regulation of glomerular hemodynamics and blood pressure (Nørregaard et al., 2015). Stimulation of EP2 and EP4 receptors can promote urinary concentration. Studies on rats with X-linked nephrogenic diabetes insipidus (XNDI) suggested that EP2 and EP4 agonists increase water channel aquaporin-2 phosphorylation and can partially compensate for a nonfunctional vasopressin type-2 receptor (Olesen et al., 2011). Another study on mice had shown that selective EP4 receptor agonists may reduce all major manifestations of XNDI, includ-
Table 1. Experimental and clinical studies on the roles of eicosanoids in the kidney diseases

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Model/Population</th>
<th>Main findings</th>
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</thead>
<tbody>
<tr>
<td>(Badr et al., 1986)</td>
<td>Rats</td>
<td>E. coli endotoxin may be responsible for decreasing eGFR and filtration fraction by stimulation of the TXA2 biosynthesis and other products of cyclooxygenase metabolism in the kidney.</td>
</tr>
<tr>
<td>(Chatziantoniou et al., 1989; Badahman &amp; Wilson, 1994; Cediel et al., 2002)</td>
<td>Rats</td>
<td>TXA2 may contribute to renal vasoconstriction. Inhibition of TXA2 production results in vasodilatation.</td>
</tr>
<tr>
<td>(Chaudhari &amp; Kirschenbaum, 1983)</td>
<td>Rabbits</td>
<td>The concentration of PGE2 in cortical tissue of kidneys is increased in AKI because of its decreased metabolism.</td>
</tr>
<tr>
<td>(Jia et al., 2012)</td>
<td>Mice</td>
<td>PGE2 increases EPO concentration and decreases anemia after renal mass reduction. It also increases the inflammatory state and provokes renal dysfunction.</td>
</tr>
<tr>
<td>(Kramer et al., 1993)</td>
<td>Rats</td>
<td>Sulotroban can stop TXA2 dependent vasoconstriction in the early phase of AKI.</td>
</tr>
<tr>
<td>(Li et al., 2009)</td>
<td>Mice</td>
<td>Selective EP4 receptor agonists may reduce all major manifestations of XNDI, including changes in renal morphology, and may become a new treatment strategy for hereditary nephrogenic diabetes insipidus.</td>
</tr>
<tr>
<td>(Makino et al., 2002)</td>
<td>Rats</td>
<td>Inhibition of EP1 receptor may prevent the progression of diabetic nephropathy.</td>
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<tr>
<td>(Mangino et al., 1987)</td>
<td>Dogs</td>
<td>12-HETE are biosynthesized in higher amounts by renal cortical tissue which undergoes rejection.</td>
</tr>
<tr>
<td>(Mederle et al., 2015)</td>
<td>Mice</td>
<td>Decreased activity of COX1 after administration of its inhibitor, called SC-560, leads to lower TXA2 concentration and protects kidneys from AKI.</td>
</tr>
<tr>
<td>(Nasrallah et al., 2014, 2016; Nasrallah et al., 2015; Nasrallah et al., 2001; Nasrallah et al., 2007)</td>
<td>Mice</td>
<td>Blockade of EP1, EP3 and EP4 PGE2 receptors may be useful in inhibiting renal damage in CKD. COX2-mPGEsynthase 1-PGE2 pathway is related to diabetic nephropathy, hyperfiltration, fibrosis, apoptosis, adiposity, dyslipidemia, and atherogenesis.</td>
</tr>
<tr>
<td>(Olesen et al., 2011)</td>
<td>Rats</td>
<td>EP2 and EP4 agonists increase water channel aquaporin-2 phosphorylation and can partially compensate for a nonfunctional vasopressin type-2 receptor.</td>
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<td>(Park et al., 2009)</td>
<td>Rats</td>
<td>20-HETE plays an important role in the development of cysts in ADPKD.</td>
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<td>(Regner et al., 2009)</td>
<td>Rats</td>
<td>Drugs that affect 20-HETE may be useful in AKI treatment. Administration of 20-HETE analogues (HEDE and HEDGE) results in better urine output and sodium excretion.</td>
</tr>
<tr>
<td>(Spurney et al., 1992)</td>
<td>Mice</td>
<td>TXA2 is an important agent in decreasing renal function in the model of lupus nephritis.</td>
</tr>
<tr>
<td>(Srivastava et al., 2014)</td>
<td>Rats</td>
<td>Higher expression of COX 2, EP2 receptor and higher biosynthesis of PGE2 lead to albuminuria due to the change in the structure of podocytes.</td>
</tr>
<tr>
<td>(Uriu et al., 1994)</td>
<td>Rats</td>
<td>TXA2 plays an important role in the progression of renal injury in diabetes by modulating renin angiotensin system and increasing urinary albumin excretion.</td>
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<td>(Vukicivic et al., 2006)</td>
<td>Rats</td>
<td>PGE2 decreases tubular necrosis and quantity of apoptotic cells via EP4 receptor. PGE 2 plays an important role in CKD mainly via both, EP 2 and 4 receptors.</td>
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<tr>
<td>(Wang et al., 2015)</td>
<td>Mice</td>
<td>Chronic kidney disease predisposes to cardiovascular accidents because of increased concentration of TXA 2.</td>
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<tr>
<td>(Wang et al., 2007)</td>
<td>Mice</td>
<td>PGI2 plays an important protective role in AKI caused by endotoxemia, by improving the function of kidneys in PGI2-cAMP-renin pathway.</td>
</tr>
<tr>
<td>(Averna et al., 2001)</td>
<td>65 patients after renal transplantation</td>
<td>Patients treated with cyclosporine have a higher cardiovascular risk because cyclosporine increases endothelium and platelet activation. Administration of drugs which may decrease or eliminate thromboxane-dependent platelet activation in vivo may provide the risk of cardiovascular events reduction in the kidney recipients.</td>
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<tr>
<td>(Courivaud et al., 2009)</td>
<td>603 renal transplant recipients</td>
<td>A G&gt;C polymorphism in COX 2 gene promoter leads to decreased COX 2 enzyme production and the concentration of PGE 2 decreases significantly.</td>
</tr>
<tr>
<td>(Dreisbach et al., 2014)</td>
<td>262 African American patients with CKD</td>
<td>20-HETE plays an important role in the development of cysts in ADPKD.</td>
</tr>
<tr>
<td>(Gainza et al., 2006)</td>
<td>38 patients on continuous renal replacement therapy</td>
<td>Epoprostenol may be used in renal replacement therapies either alone or with heparin.</td>
</tr>
<tr>
<td>(Imanishi et al., 1990)</td>
<td>5 patients with chronic vascular rejection after kidney transplantation</td>
<td>Thromboxane A2 synthetase inhibitor, called OKY-046, improved graft function after chronic rejection of kidney.</td>
</tr>
</tbody>
</table>
Klawitter et al., 2014
110 patients with ADPKD
Blockade of 20-HETE production can be a useful strategy in treatment of ADPKD.

Koyama et al., 2015
112 CKD patients
Beraprost sodium - PGI2 analogue may improve renal function in patients with CKD suffering from glomerular disease and nephrosclerosis.

Smith et al., 1992
11 male cyclosporine-treated renal allograft recipients with toxicity symptoms during treatment
Inhibiting the biosynthesis of thromboxane might decrease the nephrotoxicity of cyclosporine.

Stepniewska et al., 2002
145 patients with CKD: on conservative treatment, on peritoneal dialysis and undergoing chronic haemodialysis
Patients on peritoneal dialysis have higher levels of 12- HETE.

(Swartz et al., 1988)
63 ESRD patients with active or recently active bleeding
The efficiency of hemodialysis with epoprostenol was as good as with heparin, in the matter of blood urea nitrogen and creatinine decrease.

The Cytochrome P-450 pathway

Cytochrome P-450 hydroxylase and epoxygenase are the final two key enzymes in the eicosanoids' production. Their activity leads to generation of 20-HETE and EETs. These enzymes are located in the renal micro-vessels. 20-HETE and EETs regulate the renal microvascular function. 20-HETE is known as the constrictor of arterial arterioles. EETs work as endothelium dependent vasodilators. They activate smooth muscle cells through their impact on large-conductance, calcium-activated K+ channels in cAMP and protein kinase A dependent mechanisms. In contrast, 20-HETE inhibits the function of these channels. 20-HETE and EETs are also known for their natriuretic function. 20-HETE inhibits activity of the Na+/K+ ATPase in the proximal tubule and the Na+-K+-2Cl− co-transporter in the thick ascending limb of Henle’s loop. EETs inhibit epithelial sodium channel (ENaC) activity in the collecting duct, lower blood pressure and have renoprotective properties (Hao & Breyer, 2007; Williams et al., 2007; Dennis & Norris, 2015; Fan et al., 2015; Imig, 2013, 2015). They are degraded by a cytosolic epoxide hydrolase. Use of an inhibitor of this enzyme, called cito 4-[4-(3-adamantan-1-yl-ureido)-cyclohexyloxy]-benzoic acid (c-AUCB), in a rat study had shown that such therapy successfully increased the concentration of EETs, improved renal blood flow and increased natriuresis (Sporaková et al., 2011). Prostaglandins and epoxyeicosatetraenoic acids also mediate the connecting tubule-glomerular feedback (CTGF). CTGF is a mechanism where an increase in sodium concentration in the connecting tubule causes
Eicosanoids play an important role in regulating physiological processes, such as the pro-inflammatory response, dilatation of vessels and signal transduction. They influence renal haemodynamics and glomerular filtration rate. Eicosanoids are also involved in the pathogenesis of chronic kidney disease (CKD), acute kidney injury, hypertension, diabetes, metabolic syndrome and cardiovascular disease (CVD), acting as paracrine and inflammatory mediators (Zhao, 2013; Zhao et al., 2015; Chen et al., 2016).

EICOSANOIDS IN THE ACUTE KIDNEY INJURY (AKI)

Hypovolemia

It has been proven that the AKI risk is higher when the nonsteroidal anti-inflammatory drugs (NSAIDs) and COX2 blockers are used. AKI caused by hypovolemia is characterized by higher activity of the renin-angiotensin cascade, which disturbs the balance between vasoconstriction and vasodilatation (Norregaard et al., 2015). PGE 2 plays an important role in AKI acting via the EP4 receptor and decreasing the quantity of apoptotic cells and tubular necrosis (Vukicevic et al., 2006). Studies in rabbits had shown that the concentration of PGE2 in cortical tissue of kidneys was increased in AKI because of its decreased metabolism. (Chaudhari & Kirschbaum, 1983). It is considered that thromboxane A2 (TXA2) could be an important agent in AKI caused by hypovolemia. Studies in rats with the use of sulotroban, which is a specific TXA2 receptor antagonist, had shown that sulotroban was able to maintain the eGFR level at physiological ranges even under hypovolemic conditions. According to the presented test, sulotroban could stop TXA2 dependent vasoconstriction in the early phase of AKI (Kramer et al., 1993). Other drugs might be the reason of hypotension-induced AKI. Iloprost is a prostacycline (PGI2) analogue. It is used in the treatment of severe peripheral arterial disease. It is useful and effective because of its vasodilatory and anti-aggregant function. However, this drug can be dangerous because of a possibility of causing renal ischaemia, which may result in nonoliguric AKI. The risk factors of this condition include smoking and low diastolic blood pressure (Uyar et al., 2016). Still, the same drug can decrease the risk of contrast induced nephropathy by 70% in patients with impaired renal function. Intravenous iloprost administration results in reversing the eGFR rate loss after contrast administration (Spargias et al., 2009). Also, 20-HETE exerts protective effect on the kidney during AKI caused by ischemia. The drugs that affect 20-HETE may be useful in AKI treatment. Administration of 20-HETE analogues to rats results in a better urine output and sodium excretion. In the rat model, 20-HETE analogues act via the blockade of sodium tubular transport (Regner et al., 2009; Roman et al., 2011).

Endotoxemia

Endotoxemia may be another reason for AKI. Studies in adult male Munich-Wistar rats had shown that an E. coli endotoxin can be responsible for decreasing the eGFR and filtration fraction. Stimulation of the TXA2 biosynthesis and other products of cyclooxygenase metabolism in the kidney are the reason for this phenomenon (Badr et al., 1986). On the other hand, it was reported in the mice model that a decreased activity of COX1 after administration of its inhibitor, called SC-560, provides lower TXA2 concentration and as a result protects the kidneys from AKI. It suggests that thromboxane A2 is responsible for the development of AKI during endotoxemia because of COX1 activation (Mederle et al., 2015). In contrast to TXA2, in the mice model, PGI2 plays an important protective role in AKI caused by endotoxemia by improving the function of kidneys in the PGI2-cAMP-renin pathway (Wang et al., 2007).

Obstructive nephropathy

Obstructive nephropathy is a type of AKI caused by the structural or functional hindrance of normal urine flow. During this state, COX2 expression is increased and prostaglandins and thromboxane are being generated. It is considered that PGE2/EP4 receptors might be a possible target in the treatment of obstructive nephropathy. Studies with mice subjected to 24h bilateral ureteral obstruction (BUO) had shown that blockade of COX2 expression results in inhibiting the down-regulation of expression of the water channel proteins aquaporin 2 (AQP2) and aquaporin 3 (AQP3) in the renal cortex of examined animals (Norregaard et al., 2005; Nilsson et al., 2012; Norregaard et al., 2015). Another study performed with wild-type mice with unilateral ureteral obstruction (UO) had shown that the EP4 receptor is a possible target in preventing fibrosis by stopping the inflammatory response (Nakagawa et al., 2012).

EICOSANOIDS IN THE CHRONIC KIDNEY DISEASE (CKD)

PGE 2 plays an important role in CKD mainly via both, the EP 2 and 4 receptors. In rat models of CKD, prostaglandins are able to increase GFR and preserve the kidney function. EP2 receptor agonist may possibly increase the survival rate of kidney while the EP4 receptor agonist provided less glomerular sclerosis, better preservation of proximal and distal tubules and blood vessels and less apoptotic cells (Vukicevic et al., 2006). It has been highlighted in mice studies that the chronic kidney disease predisposes to cardiovascular accidents because of increased concentration of TXA 2 which activates its receptors and contributes to the generation of reactive oxygen species (ROS). This results in bigger endothelial activation, leads to microvascular remodeling and might be the reason of cardiovascular accidents (Wang et al., 2015). Another study on mice had shown that TXA2 is an important agent in decreasing the renal function in the model of lupus nephritis. Administration of TXA2 receptor blocker led to higher GFR rate. The use of GR32191-TXA2 receptor specific antagonist reduced the severity of proteinuria and interstitial inflammation. It also decreased the concentration of thromboxane A2 metabolites in urine, similarly to the quantity of IgG glomerular deposits (Spurney et al., 1992). TXA2 is mainly synthesized in the blood platelets and leads to their activation, aggregation and vasoconstriction. It is also produced by the kidney mesangial cells and podocytes. In glomerulonephritis, cyclosporine overdose or kidney graft rejection, it causes a decrease in renal blood flow due to afferent and efferent arterioles constriction, contraction of mesangial cells, injury of the endothelium, deposition of fibrin and extracellular matrix proteins in glomeruli and mesangium, and the progression of kidney failure. Patients with CKD have higher
plasma TXA2 concentrations than healthy individuals. As a result, patients in advanced stages of CKD are predisposed to thrombotic events and accelerated arteriosclerosis. The concentration of TXA2 also depends on the type of renal replacement therapy in the end-stage renal disease (ESRD). Haemodialysis treatment causes considerable decrease in the TXA2 level which appears to be lower than in peritoneal dialysis (PD) and in conservatively treated patients. It is caused by increased oxidative stress during the haemodialysis procedure and platelet impairment in the uremic environment (Zhao & Lint, 2014; Stepniewska et al., 2017).

TRK-100STP, which is a form of drug called Beraprost, a sodium-PGI2 analogue, may improve renal function, especially in patients with CKD suffering from glomerular disease and nephroporesis. TRK-100STP is considered to have a potential therapeutic effectiveness (Swartz et al., 1988; Koyama et al., 2015). Another PGI2 analogue – epoprostenol – is regarded as a possible anti-thrombotic factor. Studies have shown that efficiency of hemodialysis with epoprostenol was equally good as the one with heparin, in the matter of blood urea nitrogen and creatinine decrease. During hemodialysis with PGI2, bleeding was reduced up to 50%, especially in the high risk cases. The incidence of hypotension was similar during treatment with PGI2 and heparin. Administration of epoprostenol did not cause significant vasodilatatory episodes. A successful completion of the full, prospectively prescribed hemodialysis with PGI 2 was slightly lower than with heparin (82% versus 93%) (Swartz et al., 1988). It was confirmed that epoprostenol may be used in the renal replacement therapies either alone or with heparin, depending on whether there is a thrombocytopenia and an increased risk of bleeding or a state of hypercoagulability (Gainza et al., 2006). Some studies with mice had shown that blockade of EP1, EP3 and EP4 PGE2 receptors may be useful in inhibiting the renal damage in CKD by slowing the progression of glomerular and tubular injuries (Nasrallah et al., 2001; Nasrallah et al., 2014; Nasrallah et al., 2015).

Diabetes

One of the main causes of CKD is diabetes, which leads to a diabetic nephropathy. PGE2 concentration in diabetes is elevated. COX2-mPGESynthase 1-PGE2 pathway is connected with diabetic nephropathy, hyperfiltration, fibrosis, apoptosis, adiposity, dyslipidemia, and atherogenesis. Moreover, this pathway plays an important role in the development of a metabolic syndrome in the mice model (Nasrallah et al., 2007; Nasrallah et al., 2016). A study with animal models had shown increased activity of enzymes catalyzing the 20-HETE generation in renal vessels in obesity and diabetes, which may be associated with the development of hypertension (Zhao et al., 2015; Chen et al., 2016).

TXA2 plays an important role in the progression of renal injury in diabetes. It modulates the renin-angiotensin system and increases urinary albumin excretion. Studies in rats with streptozocin induced diabetes indicated that inhibition of the EP1 receptor may prevent the progression of diabetic nephropathy. Inhibition of this receptor leads to decreased mesangial expansion, decreased transcriptional activation of transforming growth factor-beta (TGF-beta) and fibronectin, and complete suppression of proteinuria. Using EP1 receptor blocker alone decreases glomerular hypertrophy and proteinuria, while using EP1 blocker and aspirin decreases mesangial expansion as well (Uru et al., 1994; Makino et al., 2002).

LOX products may also play a role in diabetic nephropathy. A study on mice with streptozocin induced diabetes had shown an increased level of 12/15 LOX and oxidative stress. It was suggested that 12/15 LOX inhibition could improve renal function by suppressing inflammation and kidney injury. One of the 12LOX products – 12-HETE is linked to development of hypertension along with diabetic nephropathy (Hao & Breyer, 2007; Klawitter et al., 2014). Patients on peritoneal dialysis, which predisposes them to higher plasma glucose concentration, have also higher levels of 12-HETE. This compound has been proven to have prothrombotic and proinflammatory properties (Zhao et al., 2015; Stepniewska et al., 2017).

ADPKD

Patients with the autosomal dominant polycystic kidney disease (ADPKD) have higher levels of inflammatory activation. It is hypothesized that increased activity of COX, LOX and CYP 450 enzymes, as well as biosynthesis of their products, remains one of the major causes of this condition. In ADPKD the production and concentration of 20-HETE is increased which is related to a lower GRF rate. An increased level of angiotensin II increases the 20-HETE concentration. It is possible that 20-HETE plays an important role in the development of cysts in ADPKD. Because of this, 20-HETE is considered as a possible biomarker of the disease. Moreover, blockade of the 20-HETE production can be a useful strategy in the ADPKD treatment in the rat model (Park et al., 2009; Dreisbach et al., 2014; Klawitter et al., 2014). Even though PGE2 increases erythropoietin (EPO) concentration, and as a result decreases the anemia after renal mass reduction, it also increases the inflammatory state and provokes renal dysfunction. In the cystic kidney rat model, it has been stated that after reduction in renal mass, there was renal blood flow reduction, elevation in blood pressure and proteinuria with no changes in GFR (Kang et al., 2000; Jia et al., 2012). It is regarded that both, the diabetic nephropathy and ADPKD, are syndromes with glomerular hyperfiltration. In these states there is an increased fluid flow shear stress which results in a higher expression of COX 2, EP2 receptor and higher biosynthesis of PGE2. In the rat model, all of these processes lead to albuminuria because of the change in the structure of podocytes (Helal et al., 2012; Srivastava et al., 2014).

EICOSANOIDS IN RENAL TRANSPLANTATION

Presence of urinary PGE2 is considered as a sign of successful renal transplantation. In contrast, a lower PGE 2 production results in a worse graft survival. A G>C polymorphism in the COX 2 gene promoter leads to a decreased expression of the COX 2 gene and thus lower COX2enzyme level results in a significant PGE 2 concentration decrease (el-Sharabasy & el-Naggar, 1991; Courivaud et al., 2009).

Moreover, there is an increased coagulative activation and biosynthesis of thromboxane during kidney transplantation. An increased 20-HETE and TXA2, synthesis is a sign of ischaemia – reperfusion injury, which is caused by increased oxidative stress during the procedure and results in a delayed graft function after the surgery (Zhao, 2013; Chen et al., 2016). It has been reported that concentration of 11-dehydro-TXB2 – which is an indicator of TXA 2 biosynthesis - is elevated after transplantation. Patients who are treated with cyclosporine have a
higher cardiovascular risk because cyclosporine may increase the activation of endothelium and as the consequence increases the level of TXA 2 and platelet activation. Drugs which decrease the thromboxane dependent activation of platelets might be considered as potentially useful in a group of patients after renal transplantation (Averna et al., 2001). Inhibiting the biosynthesis of thromboxane might decrease the nephro toxicity of cyclosporine (Smith et al., 1992). Administration of thromboxane A2 synthetase inhibitor called OKY-046, has improved the graft function in chronic kidney rejection. It also decreased proteinuria (Iamanishi et al., 1992).

A study in dogs with renal allotransplantation had shown that the LOX products, such as 12-HETE, are biosynthesized in higher amounts by renal cortical tissue which undergoes rejection. This suggests that these products may also take part in the rejection process (Mangino et al., 1987).

CONCLUSION

Lipid and lipid-derived metabolites play an important role in the physiology and pathological processes in the kidneys. They are promising biomarkers in detecting acute kidney injury, nephropathy, glomerulonephritis, and early stages of diabetic nephropathy, especially in the context of their participation in the inflammatory processes and oxidative stress. They may be considered as potential novel targets of therapy. However, the role of eicosanoids is still not fully clear and needs to be further explored in the future studies.

REFERENCES


