Protection of nitro-fatty acid against kidney diseases

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Wang W, Li C, Yang T. Protection of nitro-fatty acid against kidney diseases. Am J Physiol Renal Physiol 310: F697–F704, 2016. First published December 30, 2015; doi:10.1152/ajprenal.00321.2015.—Nitrated derivatives of unsaturated fatty acids are endogenously formed under oxidative and nitrative stress condition and are defined as electrophilic fatty acids containing a nitro group to a carbon-carbon double bond. Among the most studied nitro derivatives of unsaturated fatty acids are nitro-oleic acid (OA-NO2) and nitro-linoleic acid (LNO2). These products exhibit novel protective actions in a variety of rodent disease models. Diverse signaling events are responsible for effects of nitrated fatty acid, including activating peroxisome proliferator-activated receptor-dependent gene expression, suppressing NF-κB-induced inflammation, inhibiting oxidative stress, and increasing both endothelial nitric oxide synthase- and Nrf2-dependent gene regulation. Nitrated fatty acids have been emerging not only as a unique class of signaling molecules produced endogenously and but also as multipotent modulators of cell signaling pathways in cardiovascular and renal diseases. In this review, we discuss biochemical properties of nitrated fatty acid and its signaling pathways in the modulation of cellular events. A major focus is to review recent knowledge of nitrated fatty acid on the treatment of kidney diseases and its therapeutic potential for inflammation and metabolic disorders, with special emphasis on acute kidney injury and diabetic kidney disease.

nitrated fatty acid; Nrf2; acute kidney injury; chronic kidney disease

SEVERAL KIDNEY DISEASES ASSOCIATED with inflammatory and metabolic responses stimulate formation of free radicals, which may cause damage to the cell plasma membrane by generating oxidized lipids, including unsaturated fatty acid. Free and esterified fatty acids, important components of lipoproteins and membranes, can be easily modified by oxidative and nitrative damage. During the past decade, it has been accepted that biomolecules produced by lipid nitration during physiological conditions are able to modulate cellular responses. Fatty acid nitration is mediated by reactive nitrogen oxides such as the nitrogen dioxide radical (·NO2), which originates from intracellular processes such as oxidation of ·NO by oxygen or superoxide. Nitrated lipid represents novel signaling mediators which lead to secondary changes in protein function via electrophilic-based modifications (52). Nitro-fatty acids (FA-NO2) are also present in the vasculature, exerting a variety of biological actions, e.g., inhibiting activation of macrophages, attenuating secretion of proinflammatory cytokines, and suppressing proliferation of vascular smooth muscle cells. Nitrated fatty acids have emerged not only as a unique class of endogenously produced signaling molecules but also as multipotent modulators of cell signaling pathways in cardiovascular and renal diseases.

The present review focuses on the cell signaling pathways and molecular mechanism of nitro-fatty acid in the prevention of kidney diseases and its therapeutic potential. Most of the evidence discussed in the present review will be relevant for acute kidney injury (AKI) and metabolic nephropathy, but references to other kidney diseases will be also made when appropriate.

General Biological Features and Signaling Pathways of Nitro-Fatty Acids

Nitration of unsaturated fatty acids is a series of chemical reactions. Through multiple mechanisms, reactive nitrogen species such as ·NO2 are added to the double bond of fatty acids, leading to regio- or stereoisomers (41). Unsatrated fatty acids are able to be nitrated by peroxynitrite, including the peroxynitrite anion (ONOO−) and peroxynitrous acid (ONOOH). ·NO2 yielding from ONOO− homolysis readily diffuses through membranes and mediates fatty acid nitration. ·NO2 reacts with unsaturated fatty acids through a radical pathway: 1) a hemolytic attack by ·NO2 on the double bond, generating a β-nitroalkyl radical; 2) the β-nitroalkyl radical combines with a second ·NO2, forming intermediate nitro/nitrite derivatives; and 3) the derivatives further convert to nitroalkenes by losing −HNO2 (Fig. 1) (1, 42). Unsatrated fatty acids can be converted to electrophilic products via nitration reactions (5, 25). The nitro group is an electron-withdrawing substituent that makes the β-carbon of the unsaturated fatty acid acyl chain lose electrons. FA-NO2 therefore will preferentially react with nucleophiles [e.g., cysteine (in
proteins and glutathione), lysine, and histidine] via Michael addition. The reaction between FA-NO₂ and nucleophilic amino acids is termed nitroalkylation, which may facilitate the reversible adduction and posttranslational modification of proteins. Nitroalkylation may cause alterations in protein conformation, structure, trafficking, and catalytic activities and thus be involved in a variety of biological responses in the cells (5, 14, 25).

Exposure of oleic acid (OA) to acidic NO₂⁻/H₂O₂, myeloperoxidase, and ONOO⁻/H₂O₂ generates OA-NO₂. ·NO₂ or peroxynitrite may isomerize arachidonic acid (AA) to nitroarachidonic acid (AA-NO₂) in a specific process wherein they function as specific lipid mediators of inflammation and could be of significance in potential pathologies, e.g., inflammatory diseases (2). Currently, studies on the anti-inflammatory action and the underlying cellular mechanism of AA-NO₂ focus on macrophages. In macrophages, AA-NO₂ exhibited anti-inflammatory properties, including release of ·NO, increased levels of cGMP, modulation of macrophage activation (53), as well as inhibition of phagocytic NADPH oxidase (16). However, the possible protective role of AA-NO₂ in kidney diseases has not yet been investigated.

Nitroalkenes are present endogenously as free, esterified, and nucleophilic-adducted species (13), and studies support FA-NO₂ formation in vivo (52) and in inflammatory models (36, 45). Following an episode of focal cardiac ischemia-reperfusion (I/R), free nitroalkene tissue levels can increase in murine hearts from undetectable to 9.5 nM for OA-NO₂ (30). This concentration is well within the range of those required for physiological signaling. Recently, evidence has shown the protective effects of OA-NO₂ in animal models of metabolic and inflammatory diseases. A broad range of signaling events are responsible for these effects (Fig. 2).

**Peroxisome proliferator-activated receptor activation.** The transcriptional factor peroxisome proliferator-activated receptor (PPAR) has been found to serve as a nuclear receptor exerting protective effects against various kidney diseases (61). PPARγ heterodimerizes with the retinoid X receptor (RXR) and binds to PPAR-responsive elements (PPRE) in the regulatory region of target genes. FA-NO₂ is able to bind all three PPAR isotypes with high affinities, potently regulating the expression of multiple PPAR target genes (31, 45). FA-NO₂ is thus emerging as a novel signaling activator based on the fact that it retains efficacy as a partial PPAR agonist in metabolic and inflammatory responses without adverse effects. Moreover, FA-NO₂ has high binding affinities for all three PPAR isotypes, with PPARγ the most robustly activated receptor (followed by α and then β/δ) (21, 31, 46, 47). This is because that PPARγ prefers more hydrophilic ligands, whereas PPARα (to a lesser extent PPARβ/δ) binds saturated, hydrophobic fatty...

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Fig. 1. Different chemical structures of nitrated oleic acid (A), linoleic acid (B), and arachidonic acid (C) and mechanisms of nitro-fatty acid (OA-NO₂) formation (D). OA can be nitrated by ·NO₂ (e.g., coming from ONOOH homolysis) through a radical pathway and form nitrated oleic acid.
acids (38). Among the highly conserved ligand binding domain of PPARs, Arg288 and Glu343 are unique to PPAR\(_\alpha\)/H9253. The position and interaction between charged amino acids, Arg288 and Glu343 in PPAR\(_\alpha\)/H9253 and NO\(_2\) in fatty acid, has been suggested for selective activation of PPAR\(_\alpha\)/H9253 by FA-NO\(_2\) (31).

Nitric oxide release. FA-NO\(_2\), as a nitric oxide (NO)- and NO\(_2\)-derived species, can induce “feedbackly” endothelial NO synthase (eNOS) expression and activity. Administration of OA-NO\(_2\) was associated with increased release of NO in endothelial cells and upregulated vasculature eNOS mRNA and protein expression (26), thus exerting protective effects associated with enhanced NO production in the vasculature. In activated macrophages, AA-NO\(_2\) downregulated expression of inducible nitric oxide synthase (iNOS), which may contribute to the physiological shutdown of inflammatory responses (53).

Suppression of oxidative reactions. The oxygenation of membrane and lipoprotein unsaturated fatty acids result in oxidative inflammatory reactions, meanwhile scavenging enzymes [e.g., superoxide dismutase, catalase, glutathione peroxidase, heme oxygenase-1 (HO-1), and peroxiredoxins] as cytoprotective responses are also induced. NO inhibits LDL oxidation (17, 40), and NO released by nitroalkenes showed an antioxidant and protective role in lipid and LDL oxidation (17, 18, 51). FA-NO\(_2\) may also modulate reactive oxidative species (ROS) stress pathways through regulating production of superoxide radicals via NADPH (NOX) isoforms or inhibiting xanthine oxidoreductase (XOR). By binding to NF-κB subunits, FA-NO\(_2\) inhibits NF-κB-dependent downstream inflammatory signaling gene expression. FA-NO\(_2\) has high binding affinities for PPAR\(_\gamma\), partially activating PPAR\(_\gamma\)-dependent metabolic and anti-inflammatory responses. FA-NO\(_2\) can also induce endothelial nitric oxide (NO) synthase (eNOS) expression and activity and increase release of NO in endothelial cells.

Inhibition of NF-κB. NF-κB is known as an important nuclear factor which regulates expression of genes encoding proinflammatory cytokines during inflammatory responses. Electrophilic FA-NO\(_2\) adducted the NF-κB p65 subunit, which inhibits binding of the p65 subunit to DNA and thus represses expression of NF-κB-dependent target genes. Addition of NF-κB p65 subunit by FA-NO\(_2\) also limits downstream proinflammatory signaling and monocyte recruitment (6).
Activation of nuclear factor E2-related factor 2. Recently, the potential role of transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and cytoplasmic suppressor protein Kelch-like ECH-associating protein 1 (Keap1) has been implicated in kidney disease. Nrf2 plays a critical role in basal activity and coordinated induction of many antioxidant genes including phase 2-detoxifying enzymes and related proteins, such as enzymes of glutathione (GSH) synthesis and transfer, quinone reductase (NQO1), epoxide hydrolase, thioredoxin, catalase, superoxide dismutase, HO-1, UDP glucuronosyltransferase, and glutamate cysteine ligase (19, 25, 30, 56).

As an inactive complex, Nrf2 bound to Keap1 (44), which is a cytoplasmic repressor molecule that facilitates Nrf2 ubiquitination. Keap1 is capable of sensing the intracellular redox state through its several reactive cysteine residues. Electrophiles modify nucleophilic cysteines on Keap1 and cause a conformational change in Keap1 with liberating Nrf2. Liberation of Nrf2 from the Keap1-Nrf2 complex leads to accumulation of the de novo synthesized Nrf2 in the cytoplasm and translocation of Nrf2 into the nucleus (29, 54). Within the nucleus, Nrf2 binds to the cis-acting DNA regulatory antioxidant response element (ARE) or electrophile response elements (EpREs) found in the 5'-flanking region of specific gene promoters, resulting in transactivating Nrf2-dependent gene transcription (9, 20, 51). Nrf2-associated intracellular antioxidant and anti-inflammatory mechanisms play an important role in defending against oxidative stress (44).

Nrf2 exhibits an important role in maintaining the function and structure of the kidney (63). Nrf2 activation is suppressed in animal models of chronic kidney diseases (27), and ablation of the Nrf2 gene exacerbates diabetes-associated oxidative stress, inflammation, and nephropathy in experimental disease models (62). The Nrf2-Keap1 pathway is therefore considered to be one of the important coordinators of cellular defense and modulators of kidney disease.

Likely by Nrf2-dependent processes, FA-NO2 reversibly reacts with protein thiols of Keap1 and induces HO-1, NQO1, and GSH biosynthetic enzyme (GCLM) expression. As seen in cultured human endothelial cells transfected with Nrf2-small interfering (si) RNA, the induction of HO-1, GCLM, and NQO1 mRNA and protein expression was significantly attenuated (22, 25). In addition, OA-NO2 was induced in many heat shock transcription factor-regulated heat shock genes (22), which indicates a novel cytoprotective signaling function of FA-NO2.

Bardoxolone methyl is the most potent activators of Nrf2 known to date (10, 48). The Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) trial suggests a beneficial effect of bardoxolone methyl in improving renal function in patients with chronic kidney diseases (CKD) and type 2 diabetes (39).

However, the Phase III BEACON trial was terminated early due to safety concerns, as bardoxolone treatment was associated with an increased rate of cardiovascular events in patients with stage 4 CKD and type 2 diabetes (8). As an Nrf-2 agonist, one of the apparent advantages of FA-NO2 compared with bardoxolone is that FA-NO2 is synthesized endogenously in the body and is therefore supposed to have an improved safety profile.

Next, we will discuss some experimental data of nitro-fatty acid in prevention of kidney diseases and its therapeutic potential.

Protection of OA-NO2 in AKI

AKI is defined as an abrupt and sustained decrease in renal function. AKI is most often multifactorial and can be caused by I/R injury, sepsis, dehydration, cardiac-pulmonary surgery, radiocontrast agents, etc. AKI is common among the critically ill, and morbidity and mortality are very high. Despite many advances in medical technology, the mortality and morbidity of AKI in the intensive care unit have not improved significantly during the past two decades (55). In current ongoing clinical trials, several emerging AKI therapy options are recently reviewed by Kaushal and Shah (23). Here, we discuss the potential therapeutic effects of OA-NO2 in I/R and LPS-induced AKI in animal models.

I/R injury. In our study of I/R-induced AKI (32), mice were subjected to bilateral renal ischemia for 30 min, followed by 24 h of reperfusion. OA-NO2 was intraperitoneally given 50 min after I/R and every 6 h during the 24-h recovery period. Administration of OA-NO2 by this method is clinically relevant as AKI is usually not recognized and diagnosed early after an insult incurred in a clinical setting. OA-NO2 treatment was associated with improved renal function as evaluated by blood urea nitrogen (BUN) and plasma creatinine. In renal morphology, tubular injury indexes, e.g., tubular necrosis, dilation of renal tubules, and luminal casts, were markedly reduced by OA-NO2 treatment.

I/R injury occurs after blood flow returns to a hypoxic area. Restoration of blood flow results in infiltration of polymorphonuclear (PMN) cells, secretion of inflammatory cytokines, and the generation of reactive oxygen species and nitrogen species. The anti-inflammatory properties of OA-NO2 was evidenced in this model by the reduced production of proinflammatory cytokines (i.e., TNF-α and IL-1β) and adhesion molecules (i.e., ICAM1). These findings indicate a direct inhibitory effect of OA-NO2 on secretion of various proinflammatory cytokines. Neutrophil infiltration in damaged tissues causes a local inflammatory response at least partially by the release of lyosomal granules including MPO. Delayed administration of OA-NO2 almost completely blocked the increased tissue MPO activity after I/R, likely suggesting a primary mechanism by which nitrated lipid protects kidney injury after I/R by inhibition of neutrophil activation.

Activated neutrophils during I/R may constitute a major source of reactive oxygen species production via NADPH oxidase, which is activated in the membranes during a respiratory burst to generate superoxide. NADPH oxidase is composed of several membrane and cytosolic subunits, among which gp91phox and p47phox are particularly important as they are involved in initiation of NADPH oxidase assembly (15). OA-NO2 was found effectively to reduce I/R-induced expression of both gp91phox and p47phox, indicating that OA-NO2 may exert a direct inhibitory effect on gene expression of NADPH oxidase (32). Reduction of NADPH oxidase expression after OA-NO2 treatment might reflect reduced neutrophil infiltration during I/R.

Consistent with this study, protection of OA-NO2 is similarly demonstrated in a murine model of myocardial I/R injury (43). Importantly, I/R increased the formation of endogenous OA-NO2 and LNO2, and administration of OA-NO2 decreased myocardial infarct size and protected left ventricular function (43). Furthermore, LNO2 is shown to be involved in ischemic...
Preconditioning, an important mechanism to protect the tissue against I/R injury, LNO2 induced mitochondrial uncoupling through electrophilic modification of adenine nucleotide translocase and uncoupling protein 2, both of which protected against I/R injury (36, 37).

Endotoxemia. AKI secondary to sepsis is highly prevalent in the intensive care unit setting, and the mortality rate can be very high. Currently, the management of sepsis and sepsis-associated acute renal failure is largely supportive. Our study (59) demonstrated an alternative option that preventive treatment with OA-NO2 attenuates systemic and local inflammation and improves multiorgan dysfunction in endotoxic animals. It indicates a therapeutic potential of OA-NO2 in endotoxemia.

OA-NO2 pretreatment improved renal function and ameliorated the renal expression of proinflammatory cytokines, chemokines, and adhesion molecules in mice with endotoxic shock induced by LPS (59). An interesting finding in the study was that OA-NO2 prevented increased iNOS and cyclooxygenase (COX-2) in endotoxic mice. NO derived from different enzymatic sources has distinct actions in endotoxemic organ failure; for example, eNOS-derived NO protects the cardiovascular system (26), whereas iNOS-derived NO mediates kidney injury in endotoxic shock (28, 60). Similar to iNOS, COX-2 is highly induced by proinflammatory stimuli. COX-2−/− mice are resistant to LPS-induced inflammation and mortality, accompanied by blunted induction of renal iNOS expression (11, 12), indicating that LPS-induced iNOS expression may be mediated by COX-2-derived products. Robust induction of renal iNOS and COX-2 in response to LPS administration was dramatically suppressed in parallel by pretreatment with OA-NO2, suggesting that nitroalkenes may be capable of directly suppressing COX-2 expression in the context of inflammation. It should be noted that OA-NO2 showed protection from LPS-induced injuries not only in the kidney but also in the liver and heart, implicating the promise of prevention and a possible therapeutic strategy for endotoxic shock.

Cisplatin-induced kidney injury. Cisplatin is a highly effective antineoplastic DNA-alkylating agent and is one of the important components in combination chemotherapy in the treatment of a number of cancers. One of the serious adverse effects of cisplatin is nephrotoxicity. A decline of renal function was found in ~25–35% patients after a single dose of cisplatin (35). Multiple factors are responsible for the pathogenesis of cisplatin-induced nephrotoxicity, among them inflammation, which plays a key role. In a recent study (57), OA-NO2 pretreatment improved renal function and prevented tubular damages in mice treated with cisplatin. The study showed evidence that beneficial effects of OA-NO2 in preventing cisplatin-induced kidney injury are at least partially through intervention of the COX-2/membrane-associated-PGE synthase (mPGES)-1/PGE2 cascade, besides the suppression of classic inflammatory factors. COX-2 converts AA to an intermediate endoperoxide, which is catalyzed by specific synthases (e.g., mPGES-1) to PGE2. PGE2 has an established role in mediating pain and inflammatory responses. OA-NO2 attenuated gene and protein expression of COX-2 and mPGES-1 as well as renal PGE2 production induced by cisplatin. Therefore, protection of OA-NO2 in cisplatin-induced nephropathy appears to be multifactorial.

Protection of OA-NO2 in Diabetic Nephropathy

The prevalence of CKD has increased in the last two decades, and it is becoming a worldwide epidemic, mainly driven by the dramatically increased incidence of diabetes and obesity. It has become urgent to search for novel targets and treatments for CKD to reduce social and economic burden of this disease in the general population (7).

Diabetic nephropathy. Diabetic nephropathy (DN) remains the leading cause of end-stage renal disease in the United States. Although substantial progress has been made toward understanding the pathogenesis of DN, such as renal inflammation, oxidation reaction, and fibrosis, at present there are no drugs that come anywhere close to providing the solutions we want for our patients. The current therapeutic strategy for treating DN mainly involves lifestyle modification, control of hyperglycemia, dyslipidemia, and systemic blood pressure (7) as well as blockade of the renin-angiotensin system (RAS). Activation of Nrf2 is a logical intervention in patients with diabetes and CKD. In animal models, OA-NO2 has demonstrated beneficial effects on obesity with the metabolic syndrome (58) and on diabetes (34, 46). As discussed above, nonselective activation of PPAR as well as anti-inflammatory and prosurvival Nrf2 signaling may at least partially account for biological effects of OA-NO2.

Following OA-NO2 treatment for 14 days, reduced food intake and body weight gain were observed in obese Zucker rats, accompanied by significantly decreased plasma triglyceride, almost normalized plasma free fatty acid, as well as increased plasma HDL (58). These metabolic effects were likely attributed to PPARα-like characteristics of OA-NO2, as PPARα agonists induce satiety and reduce body weight gain. Proteinuria was markedly ameliorated in response to OA-NO2 treatment in Zucker rats, indicating an improvement of podocyte function in this obesity model, although further data (e.g., podocyte markers) were not presented in the study. It is reasonable to assume that PPARγ subtype activation may at least partially contribute to some aspects of OA-NO2 action, as for example the effects of lowering lipid and proteinuria in this obesity model. OA-NO2 has also been shown to significantly improve hyperglycemia in diabetic ob/ob mice that was comparable with the use of rosiglitazone (46). Administration of OA-NO2 over a period of 4 wk significantly normalized blood glucose and insulin levels. Glucose and insulin tolerance tests also showed improved glucose handling and increased insulin sensitivity in diabetic mice with OA-NO2 treatment. OA-NO2 improves DN at least partially via modulation of matrix metalloproteinase (MMP). Serum and urinary MMP levels are shown to be increased in diabetic patients (49), and a positive correlation between degrees of albuminuria levels of urinary MMP-9 has been observed (50). An elevated serum MMP-7 level is inversely correlated with renal function in proteinuric diabetic patients (3). Interestingly, during inflammation OA-NO2 first activates pro-MMP proteolytic activity, promoting cell remodeling and migration to the site of injury, and then transcriptionally inhibits MMP expression by activation of PPARγ, thereby limiting the further progression of inflammatory processes (4).

RAS blockade with ACEi and ARB has shown to attenuate glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria. Our recent study demonstrated the efficacy of combining
OA-NO2 with ARB to halt the progression of DN in db/db mice (34). Compared with single treatment, dual treatment with both OA-NO2 and ARB more significantly reduced glomerulosclerosis scores, paralleled with reduction of proteinuria, preservation of podocyte number, and suppression of profibrotic extracellular matrix marker production. The favorable effect of the combined therapy was likely attributed to more robust suppression of oxidative stress and inflammation by OA-NO2 and ARB. These findings suggest that synergistic effects of OA-NO2 and ARB may lie in their different targets in the DN signaling pathway, providing a reasonable rationale for future clinical studies on the therapeutic strategy in patients with type 2 diabetes. However, more extensive experiments are warranted to validate specific mechanisms of OA-NO2 action and to clarify its safety profile before clinical trials in humans.

Notably, an adverse side effect of rosiglitazone, weight gain, reflecting both edema and adipogenesis, was not seen in OA-NO2-treated animals (46, 58), as opposed to rosiglitazone treatment. In 3T3-L1 adipocytes, rosiglitazone but not OA-NO2 stimulated RNA transcription and translation of the PPARγ-regulated gene aP2. This gene encodes fatty acid trafficking protein, which mediates early and late stages of adipogenesis and thus affects adipocyte number and triglyceride content. In fact, rosiglitazone induced greater extents of adipocyte lipid accumulation than OA-NO2 (46), which is consistent with different aP2 expression in those adipocytes. These observations suggest that OA-NO2 may offer a safe therapeutic intervention for obesity and obesity-related conditions compared with thiazolidinediones.

Protection of OA-NO2 in nephrotic syndrome. Adiamycin (ADR)-induced nephrotic syndrome is a widely accepted animal model which mimics human focal glomerular sclerosis. OA-NO2 markedly improved albuminuria, hypoaalbuminemia, hyperlipidemia, and renal function in mice treated with ADR. OA-NO2 attenuates ADR-induced glomerulosclerosis, podocyte loss, and tubulointerstitial fibrosis, likely due to suppression of oxidative stress and inflammation in the kidney (33). These findings support the therapeutic potential of OA-NO2 for management of human glomerular disease, such as focal segmental glomerulosclerosis.

Perspectives

Although beneficial effects of NO2-FA have been demonstrated in various animal models, the safety issue of FA-NO2 must be rigorously tested. So far, there are no studies evaluating the potential toxicity of this compound, in particular, when administered for longer periods of time. Currently, a randomized, double-blind, dose-rising study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of CXA-10, the first FA-NO2 approved by the US Food and Drug Administration, in volunteers are underway, aiming to treat AKI related to the administration of contrast imaging agents (clinicaltrials.gov ID: NCT02127190). An encouraging finding from the Phase 1 study is a wide therapeutic window for FA-NO2. CXA-10 was very well tolerated in obese and healthy people. The completion of the study will provide more evidence of the therapeutic potential of OA-NO2 for the management of human kidney diseases.

Conclusion

NO2-FAs are by-products of NO- and NO2-dependent oxidative reactions. These species reduce oxidant stress and inflammation in a variety of models of inflammatory injury and metabolic syndrome. A broad range of signaling events may contribute to these effects, including increasing Nrf2-dependent gene expression, inhibiting NF-kB-induced inflammatory responses, and activating PPAR-dependent gene expression. In animal models, the administration of NO2-FAs has demonstrated benefits in I/R or endotoxin-mediated renal injury, nephritic syndrome, diabetic kidney diseases, and obesity with metabolic syndrome. In light of the nature of an endogenous product, NO2-FA may offer an effective and safe therapeutic intervention for various kidney diseases. Strong experimental data call for clinical trials for testing the renal therapeutic potential of NO2-FA.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

Author contributions: W.W. and T.Y. prepared figures; W.W., C.L., and T.Y. edited and revised manuscript; W.W., C.L., and T.Y. approved final version of manuscript.

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